# ASSESSMENT OF PHARMACOVIGILANCE SYSTEM OF NEW DRUGS IN THAILAND

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นิสิตตรา พลโคตร : การประเมินระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ในประเทศไทย. ( ASSESSMENT OF PHARMACOVIGILANCE SYSTEM OF NEW DRUGS IN THAILAND) อ.ที่ปรึกษาหลัก : รศ. ภญ. ร.ต.ท. หญิง ดร. ภูรี อนันตโชติ, อ.ที่ปรึกษาร่วม : ดร. ภก.โอสถ เนระพูสี

การศึกษาส่วนใหญ่ประเมินระบบเฝ้าระวังความปลอดภัยการใช้ยาภายหลังออกสู่ตลาดของยาทั่วไป ซึ่งไม่มีการศึกษาเกี่ยวกับระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ทั้งระบบตั้งแต่ขั้นตอนก่อนออกสู่ท้องตลาดจนกระทั่งถึงขั้นตอนหลังออกสู่ท้องตลาด ประเทศไทยมีการปรับแนวทางการเฝ้าระวังความปลอดภัยการใช้ยาใหม่ตามระดับความเสี่ยง (safety monitoring program: SMP) ในปี 2560 และบังคับใช้แผนจัดการความเสี่ยง (risk management plan: RMP) กับยาชีววัตถุบางประเภทเมื่อปี 2560 หลังจากการเปลี่ยนแปลงเหล่านี้ยังไม่มีหน่วยงานใดทำการประเมินผลระบบเฝ้าระวังความปลอดภัยโดยเฉพาะยาใหม่เลย ดังนั้นการศึกษานี้มีวัตถุประสงค์เพื่อศึกษาระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ในประเทศเป้าหมายและเพื่อประเมินระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ในประเทศไทย วิธีการดำเนินการวิจัยใช้วิธีการทบทวนวรรณกรรมอย่างเป็นระบบ และสืบค้นอย่างเป็นระบบจากเวปไซต์ของหน่วยงานราชการของประเทศเป้าหมายได้แก่ ประเทศที่มีรายได้สูง 83 ประเทศ และประเทศที่มีรายได้ปานกลางค่อนข้างสูง 56 ประเทศ และทำการสัมภาษณ์เชิงลึกผู้เกี่ยวข้องกับระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ 3 กลุ่มเป้าหมายได้แก่ เภสัชกรสำนักงานคณะกรรมการอาหารและยา (อย.) เภสัชกรบริษัทยา เภสัชกรและแพทย์ประจำโรงพยาบาล ผลจากการทบทวนวรรณกรรมอย่างเป็นระบบจาก 139 ประเทศ พบว่า 87 ประเทศมีระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ในจำนวนนี้ 30 ประเทศ (34.48%) กำหนดเงื่อนไขให้บริษัทยาดำเนินการเฝ้าระวังความปลอดภัยการใช้ยาใหม่แบบเชิงรุกภายในระยะเวลาที่กำหนด และพิจารณาอนุมัติปลดยาใหม่ออกจากเงื่อนไข ประเทศส่วนใหญ่ดำเนินการในลักษณะนี้เป็นประเทศที่มีรายได้สูง 28 ประเทศ และประเทศที่มีรายได้ระดับปานกลางค่อนข้างสูง 2 ประเทศ (ประเทศบัลแกเรียและประเทศไทย) จากการสัมภาษณ์เชิงลึกผู้มีส่วนเกี่ยวข้องกับระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ 36 คน (เภสัชกร อย. 6 คน เภสัชกรบริษัทยา 6 คน เภสัชกรโรงพยาบาล 16 คน และแพทย์โรงพยาบาล 8 คน) พบว่า บริษัทยาให้ความร่วมมือในการยื่น RMP ด้วยข้อมูลที่ครบถ้วนและปรับปรุงข้อมูลความปลอดภัยกรณีพบความเสี่ยงใหม่ แต่ยังไม่มีระบบติดตามความร่วมมือของบริษัทยาในการดำเนินการตามสิ่งที่เขียนไว้ใน RMP บริษัทยาและโรงพยาบาลให้ความร่วมมือในการรายงานอาการไม่พึงประสงค์จากการใช้ยา และอย.ให้ความเห็นว่ารายงานที่ส่งเข้ามามีคุณภาพดี ด้วยข้อมูลที่ครบถ้วน โดยผู้รายงานแจ้งทั้งอาการไม่พึงประสงค์จากการใช้ยาที่รุนแรงและไม่รุนแรงตามระยะเวลาที่กำหนด แต่ทั้งนี้พบว่ามีจำนวนรายงานอาการไม่พึงประสงค์จากยาใหม่ค่อนข้างต่ำ ไม่เพียงพอในการตรวจจับสัญญาณความเสี่ยงและไม่เพียงพอในการพิจารณาอนุมัติปลดยา SMP รวมทั้งการสื่อสารความเสี่ยงยังไม่ครอบคลุมถึงบุคลากรทางการแพทย์ทุกคน โดยสรุปผล ประเทศไทยมีโครงสร้างระบบเฝ้าระวังความปลอดภัยการใช้ยาใหม่ที่เทียบเท่ากับกลุ่มประเทศที่มีรายได้สูง เภสัชกร อย.และเภสัชกรบริษัทยามีความเข้าใจในแนวทางการเฝ้าระวังความปลอดภัยการใช้ยาใหม่เป็นอย่างดี ขณะที่โรงพยาบาลขาดความเข้าใจในแนวทางการเฝ้าระวังความปลอดภัยการใช้ยาใหม่ การให้ความสำคัญกับยาใหม่ไม่แตกต่างจากยาทั่วไป

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| สาขาวิชา | เภสัชศาสตร์สังคมและบริหาร | ลายมือชื่อนิสิต ..... |
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Previous studies evaluated pharmacovigilance (PV) system in term of passive surveillance in only post-marketing phase and did not specify new drugs. None study reviewed PV system of new drugs from pre-marketing phase to post-marketing phase. In addition, the situation of new safety monitoring program (SMP) risk-based approach integrated with risk management plan (RMP) was unknown. The objectives of the study were to review pharmacovigilance system of new drugs in targeted countries and to assess pharmacovigilance system of new drugs in Thailand. Method of the first objective was systematic review and primary data sources were drug regulatory authority websites in 83 high income countries and 56 upper-middle income countries. Method of the second objective was in-depth interview. Results of the first objective, a total of 139 countries, 87 countries had performed PV of new drugs. Thirty countries (34.48%) required new drugs with condition to conduct post-authorization safety studies within pre-specified monitoring period and processed risk assessment to remove new drugs from condition. Of these, 28 countries were high-income countries and 2 countries were upper-middle income countries (Bulgaria and Thailand). Results of the second objective, a total of 36 key informants were interviewed including 6 pharmacists from Thai FDA, 6 pharmacists from drug companies, 16 pharmacists and 8 physicians from hospitals. The achievable issues of RMP were that the compliance of drug companies was good in RMP submission as well as RMP update. The unachievable issue of RMP was that there was no PV inspection. The achievable issues of SMP were that the compliance of drug companies and hospitals was good in reporting complete ADR information, reporting all types of ADR following timetable. The unachievable issue of SMP was that the local data source was insufficient to process signal detection and support to remove new drugs from SMP. Risk communication did not reach all healthcare professionals. Conclusions: Performance of PV new drugs in Thailand was equal to high income countries. Overall, Thai FDA and drug companies understood RMP, SMP and could comply following guideline. Hospitals did not understand SMP guideline. The importance of differentiation of new drugs from non-new drugs was less emphasized.



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| | | Co-advisor's Signature ..... |

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Nisittra Polkot

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# CHAPTER I

# INTRODUCTION

## Background and Rationale

New drugs launched into the market have continued to increase every year. In 2019, the United States approved 47 new active substances followed by Japan (33 items), Canada (30 items), Switzerland (28 items), EMA (27 items) and Australia (25 items). During 2015 to 2019, the total number of approved new active substances in these 6 regulatory agencies was 1026. Of these, the United States had the largest number of approved new active substances at 22% whereas 14-16% were authorized in other regulatory agencies (1). Safety of a new drug is evaluated and monitored through the pre-marketing approval system and the post-marketing surveillance system. At the time of marketing authorization, the regulatory authorities basically review the efficacy, safety and quality of approved drugs relying upon information from clinical trials (2). However, there are some limitations in the clinical trial process such as small number of participants, relatively short study duration which results in limited ability to detect rare or serious adverse drug reactions (ADRs). Moreover, special population groups including pediatric, elderly, pregnant and lactating women are excluded from these trials. Patients receiving co-medications or suffering from co-diseases are also usually excluded. Not all ADRs can be identified in the clinical trials phase. Especially, some new drugs are approved by fast track-process. Therefore, there

is a requirement to continuously rigorous monitor the safety from pre-marketing phase through post-marketing phase (3). Pharmacovigilance are the activities which identify, evaluate, and protect ADRs throughout the whole period of a medicinal product's life cycle. If the pharmacovigilance system is well established, it can assist to decrease and preclude ADRs (4).

From the thalidomide tragedy in the 1960s, this has resulted in the enormous alteration to drug regulation worldwide. Subsequently, several countries revolutionized their pharmacovigilance system of newly approved drugs. Originally, spontaneous reporting system is a passive surveillance used to identify ADRs. In 1968, World Health Organization (WHO) established a program for international drug monitoring. WHO provides basic requirements including risk collection, risk assessment and risk communication as a pharmacovigilance system framework. Basically, healthcare professionals and pharmaceutical companies collect ADRs by using spontaneous reporting system to national pharmacovigilance center. The Yellow card scheme of the United Kingdom in 1964 (5), Blue card for Australia in 1964 (6), and MedWatch from the United States in 1969 are examples of spontaneous reporting system (7). However, the known weaknesses of the spontaneous reporting system are under-reporting, incomplete information and delay in identification of ADRs.



The concept of active surveillance was introduced during 1970-1980 which required that new drugs with conditions are requested to conduct post-authorization safety study (PASS) within a pre-specified monitoring period. PASS can deal with the

weaknesses of the spontaneous reporting system. The advantages of active surveillance include earlier identification of ADR and stronger evidence for safety of new drugs. Observational studies and post-marketing clinical trials are PASS operated by pharmaceutical companies. Prescription event monitoring is the example for active surveillance which was initiated in New Zealand in 1977 (8), the United Kingdom in 1980 (9), and Japan in 1997 (10).

Safety of new drugs is crucial to monitor from pre-marketing phase to post-marketing phase. Active surveillance and passive surveillance are post-marketing phase. However, there is no plan at the time of approval. Therefore, the pharmacovigilance has been developed to highlight proactive surveillance in the 2000s to complement both active and passive surveillance (3).

Risk management plan (RMP) is a strategy beyond the existing pharmacovigilance system. RMP is a proactive systematic approach which is set up to rapidly identify, monitor and minimize risk in advance prior to taking new drugs. RMP is mandated at the time of authorization and updated over time. In addition, RMP is the tool to ensure benefit-risk balance of new drugs throughout the drug product life cycle. Particularly, the additional pharmacovigilance activities and the additional risk minimization activties are required for new drugs (11). The international conference on harmonization (ICH) launched RMP in 2004. The founding regulatory ICH members include the European Union, the United States and Japan which adopted the guideline in 2005, 2007 and 2013, respectively (12, 13).

Basically, RMP consists of three main components including safety specification, pharmacoviglance activities and risk minimization activities. Safety specification includes important identified risks, important potential risks and important missing information. Pharmacovigilance acitivities consist of routine activities such as spontaneous reporting system and additional activities such as PASS. Risk minimization activities comprise routine activities which include package leaftlet and summary of products characteristics as well as additional activities like educational sessions for healthcare professionals and patients, together with guideline for physicians and pharmacists, and patients' brochures. At pre-marketing phase, pharmaceutical companies have responsibilities to prepare and submit the RMP to regulatory authorities to review and approve the RMP. At post-marketing phase, pharmaceutical companies must report the progression of implemented activities mentioned in the RMP and update the RMP if new safety issues have occurred. Furthermore, regulatory authorities process inspection of the compliance of pharmaceutical companies (14, 15).



Thailand established national pharmacovigilance center in 1983 (16). The pharmacovigilance system of new drugs in Thailand is the safety monitoring program (SMP) which was started in 1991 and aims to monitor new drugs including both chemical products and biological products among Thai patients (17). According to previous study, the method of monitoring the SMP and non-SMP were similar by using passive surveillance in drug companies and hospitals (18). There had been low

proportion of adverse events reported for new drugs which was not enough to identify signal (19). There was lack of understanding among healthcare professionals about the SMP (20). Later, a new SMP regulation was introduced in 2017. The concept is that new drugs including chemical medicines and biologic products are monitored depending on their risks. Risk level 1 are new drugs approved with clinical trial phase 2, required to conduct active surveillance for at least 2 years. Risk level 2 are new chemical entities, new indications, new combinations and new biologic products desiring intensified reporting for 2 years. Risk level 3 are new route of administrations, new dosage forms, new delivery systems and new strengths requesting intensified reporting for 1 year (21). Additionally, Thailand announced RMP for new biologic products, biosimilars, botulinum toxin and erythropoietin in 2017. The RMP is a legal requirement which is performed on top of SMP (22).

Previous studies reviewed pharmacovigilance system in term of passive surveillance at post-marketing phase and did not address about new drugs (23-27). None of the studies reviewed pharmacovigilance system of new drugs. Therefore, this study intended to review the pharmacovigilance system of new drugs in targeted countries. The situation of new drugs in Thailand was previously assessed following the former SMP guideline. The evidence when the new SMP risk-based approach guideline was integrated with RMP was unknown in Thailand. Therefore, this study investigated the current situation of the pharmacovigilance system of new drugs in

Thailand. Specifically, how each stakeholder takes action on monitoring safety of new drugs. The findings of this part contributed to know whether the activities reached the purpose of RMP and SMP. The scope of the study covered pharmacovigilance of new drugs from the time of authorization and throughout the post-marketing phase. The study did not explore pharmacovigilance in the clinical trial phase.

**Objectives of this study**

1.To review pharmacovigilance system of new drugs in targeted countries

2.To assess pharmacovigilance system of new drugs in Thailand

**Expected benefits from this study**

The results of the first objective provide information on the components of pharmacovigilance system of new drugs and the performance of pharmacovigilance system of new drugs in Thailand compared to other countries.

The results of the second objective provide information on the effectiveness of the pharmacovigilance system of new drugs in Thailand in order to further reinforce and develop the system. Furthermore, the findings will support the policy makers to improve regulation.

# CHAPTER II

# LITERATURE REVIEW

The literature review of this study provides the regulatory basis and research findings relating to pharmacovigilance system of new drugs. The contents are categorized as follows:

-New drug issues and safety concerns
-Pharmacovigilance system
-Relevant stakeholders in pharmacovigilance system and their responsibilities
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    -Uppsala monitoring center
    -National pharmacovigilance center
    -Pharmaceutical companies
    -Healthcare professionals
    -Patients
-Pharmacovigilance methods
    -Passive surveillance
    -Active surveillance
    -Proactive surveillance
-Safety monitoring program (SMP) in Thailand
-Pharmacovigilance assessment framework and indicators
    -Donabedian framework
    -Pharmacovigilance indicators
        -Indicators-based pharmacovigilance assessment tool (IPAT)
        -World health organization (WHO) indicators
-Thailand safety monitoring program (SMP) indicators
-Performance of pharmacovigilance system across the globe
-Performance of pharmacovigilance system in Thailand

**New drug issues and safety concerns**

New drug authorization has tended to continuously increase every year. In 2019, the United States approved 47 new active substances followed by Japan (33 items), Canada (30 items), Switzerland (28 items), EMA (27 items) and Australia (25 items) (1). At the time of marketing authorization, the drug regulatory authorities basically review efficacy, safety, and quality of new drugs, although there are some limitations in the pre-marketing phase. First, trials in animals are inadequate to anticipate human safety. Second, there are a small number of participants in the clinical study that is less than 3,000. Third, clinical trials are conducted in short duration that is less than 3 years which may not be able to detect rare adverse drug reactions. Fourth, special population including pediatric, elderly, pregnant and lactating women are excluded. Finally, patients receiving co-medications or suffering from co-diseases are also usually excluded. After new drug approvals, they are used in an enormous number of various patients with co-medicines with access to those drugs for a long duration. This phase has led to reveal new, rare, and serious ADRs. Therefore, it is necessary to continuously monitor medicinal products during post- authorization (2).



Safety of a new drug is evaluated and monitored through the pre-marketing approval system and the post-marketing surveillance system. For safety issue in pre-marketing approval system, a common technical document (CTD) is the application dossier for the authorization of new drugs. It contains safety information about nonclinical trial and clinical trial (28). Furthermore, risk management plans are also

required at the time of authorization, and these are amended over time (11). For post-marketing surveillance, all medicinal products are basically monitored using passive surveillance as spontaneous reporting system (3).

Particularly, new drugs need active surveillance by intensive monitoring and proactive surveillance to complement the existing system (29). The European Union has announced new medicines that should receive additional monitoring which include new active substances and biological products (30). In Japan, the new medicinal products are subject to intensive monitoring in early post-marketing phase vigilance (EPPV) which includes the new active substances, the new combinations, the new dosage regimens, the new administration routes and the new indications (31). In Thailand, new drugs containing the new chemical entities, the new indications, the new combinations, the new biological products, the new delivery systems, the new route of administrations, the new dosage forms and the new strengths are monitored by using stimulated reporting (32).



**Pharmacovigilance system**

Pharmacovigilance system is the interconnection related to pharmacovigilance activities among relevant stakeholders including World Health Organization, Uppsala monitoring center, national pharmacovigilance center, pharmaceutical companies, healthcare professionals and patients. Pharmacovigilance activities consist of identification, evaluation, and prevention of adverse drug reactions. Pharmacovigilance system initiated from new medicines development through post-marketing phase.

Generally, pharmacovigilance system covers all health products which are medicines, herbals, biologicals, medical devices, blood products, vaccines and complementary by using passive surveillance (4, 33). Pharmacovigilance system of new drugs is a subset of pharmacovigilance system. It is required to intensively monitor by using active surveillance and proactive surveillance to complement passive surveillance (29).

**Relevant stakeholders in pharmacovigilance system and their responsibilities**

**World Health Organization (WHO)**

WHO established the program for international drug monitoring in 1968 due to thalidomide disaster that occurred in the 1960s. The WHO headquarter is located in Geneva, Switzerland and is responsible for policy. The purposes of conducting this program are to encourage establishment of national pharmacovigilance center in countries worldwide, to provide guideline on drug safety, to improve patient safety in association with medicine uses and to facilitate the education and training in pharmacovigilance of healthcare professionals and the public (4). Pharmacovigilance is required in every country due to differences in diseases, genetics, diet, drug distribution and drug use. Information derived in one country may not be applicable in other parts of the world, with different situations (34). The first ten countries that participated in this program included the United States, the United Kingdom, Sweden, New Zealand, the Netherlands, Ireland, Germany, Czechoslovakia, Canada and Australia (35). Later, the network of performing pharmacovigilance centers has significantly extended to countries worldwide. The last updated on July 2021, showed that 171 countries are

the part of the WHO program for international drug monitoring which includes 148 countries as the full member and 23 countries as the associate member (36). Thailand became the 26th full member of WHO international drug monitoring in 1984 (19).

**Uppsala monitoring center**

Uppsala monitoring center is the operational center of the WHO collaboration for international drug monitoring. It was founded in 1978 as an independent, non-profit foundation in Sweden. The Swedish government provided budget for this center. The major responsibility is to collect and operate the international individual case safety report (ICSR) obtained from national pharmacovigilance centers which are the members of WHO program for international drug monitoring. These ICSR are reviewed, screened and then recorded into the WHO Vigibase. Signal are identified by professional consultants who are the specialists in each area. Safety information is disseminated through the adverse drug reaction newsletter issued 4 times per year consisting of regulatory actions of safety concerns and this is globally circulated to national pharmacovigilance centers. Education and training courses in pharmacovigilance are also provided to staff of national pharmacovigilance center (37). Moreover, course lectures of pharmacovigilance training are performed on the Uppsala monitoring center YouTube channel. Uppsala monitoring center also collaborates with international research to support signal evaluation such as the observational medical outcome partnership (OMOP) project carried out by the US FDA and the pharmacoepidemiologic research on the outcomes of therapeutics by the European

consortium (PROTECT). In addition, “Talk and Tell” application for smartphone was introduced in 2015 to support the patients to report adverse drug reactions. The Uppsala monitoring center web page provides access to the safety information (38).

**National pharmacovigilance center**

The global obligations of national pharmacovigilance centers comprise collecting case reports of adverse drug reactions, detecting and evaluating potential signals, making decision, taking regulatory action, and alerting healthcare professionals, manufactures and public to new risk of drugs. Signal collection is obtained from passive and active surveillance. Decision making and regulatory action are processed by the scientific committee. The regulatory actions are classified into withdraw medicinal products, restricted usage, and changing of label or warning (39). Communication information to healthcare professionals of drug safety issues is a pivotal procedure. The crucial consideration is how rapidly data needs to be conveyed to healthcare professionals and communities. An immediate communication is required for a newly serious adverse reaction. Currently, there are several channels to message drug safety to the relevant recipients including hard copy bulletin, websites or direct electronic mail (40, 41).



National pharmacovigilance centers in developed countries such as the United States, the European Union, the United Kingdom, Canada and Japan are well established in policy, database system and inspection (42-44). Especially in annual funding for post-market studies, the United States and Canada provide high budget for

these approximately $10 million or more. The United Kingdom contributes $2 to10 million. However, the European Union dedicates less than $2 million (43). In low and middle-income countries, the lack of training and lack of financial provision were found to be the major obstacles of pharmacovigilance system (45).

**Pharmaceutical companies**

Pharmaceutical companies are responsible for pharmacovigilance throughout a drug product's life cycle. The core activities include preparing the safety profile for suitable use of new active substances and proper communication for example summary of product characteristics or patient information leaflet to patients as well as guidance for healthcare professionals (46), attending to the procedure of signal collection using passive and active methods, submitting risk management plan of new drugs for assuring the benefit-risk balance of the medicinal products after launching as well as maintaining inspection (47). In addition, the risk management plan must be updated in order to know whether there are new ADRs which affect the balance of benefit-risk. Periodic safety update report (PSUR) needs to be submitted at the defined time point. Finally, the pharmaceutical companies have to arrange the qualified person responsible for pharmacovigilance to deal with regulatory authorities (48).



**Healthcare professionals**

Healthcare professionals are important stakeholders to report adverse drug reactions in clinical trial phase and post-marketing phase. For post-marketing phase, it is voluntary in most countries. Some countries mandate healthcare professionals to

report adverse drug reaction such as Indonesia, Japan, Korea, Malaysia, Philippines Switzerland and Vietnam (49). Under-reporting from healthcare professionals is a problem. According to the systematic review worldwide of factors which influenced under-reporting, the reasons for not reporting are fear of possible legal entailment, lack of time to find and complete reporting form, ignorance about the importance of reporting, belief that only safe drugs are supplied to the market and guilt for providing treatment which makes risk to the patients. In Thailand, healthcare professionals' ADR reporting is voluntary. The barriers to report adverse drug reactions under SMP include lack of collaboration among healthcare professionals, uncertainty in causality and lack of time. Pharmacist is the main stakeholder responsible for report adverse events of new drugs under SMP (20).

Normally, for established drugs, only unexpected and serious ADRs need to be reported. In EU, medicinal products under additional monitoring were displayed with inverted black triangle on package leaflets and summary product characteristics for new active substances or biosimilars, new combinations, new route of administrations, new delivery systems or established medicines used in new population. The aim of inverted black triangle was to notify that safety profile of these new medicinal products was not fully established, requiring all adverse events should be reported. Healthcare professionals' awareness of additional monitoring in UK oncology were surveyed. Most oncology pharmacists (87%) knew that new medicines with inverted black triangle should be reported all ADRs whereas 55% of nurses and 38% of oncologists were

aware of this issue. The behavior on ADR reporting did not alter whether the medicines had presence or absence of inverted black triangle (71% of oncologists, 64% of nurses, 39% of pharmacists) (50). This UK study was consistent with research in Ireland that most of healthcare professionals were aware of the concept of inverted black triangle. Particularly, pharmacists had the highest awareness of inverted black triangle (86.4%) compared with general practitioners (35.6%), hospital doctors (35.1%) and nurses (14.9%) (51).

**Patients**

Patients were allowed to directly report adverse drug reaction to the national pharmacovigilance center in several countries such as the United States in 1993, the Netherlands in 2003, and the United Kingdom in 2005 (52). In 2012, patient involvement in reporting was available in 44 countries worldwide. The adverse drug reactions of patients reporting differ from healthcare professionals reporting in term of severity level of adverse drug reactions. The patients seem to report mild adverse drug reactions. One important feature of patient report was the subjective explanation of adverse drug reactions. This contributed to complement healthcare professionals reporting. The information of patient reporting was enough to generate new safety signals (53).



As the results from systematic review, the obstacles of patients reporting were that they do not know the adverse drug reaction reporting system such as where or who to report to, lack of re-response from submitted reports, complication of reporting

process and postal costs. The motivations which influence patients to report included that they required to distribute their experiences to communities. Serious adverse drug reactions were more likely to be considered to be reported. Individual feedback was requested to ensure that the reports were received. Reporting procedures and forms were needed to be convenient to access and complete (54). Thailand had permitted patients to report adverse drug reactions in 2010 through their website of health product vigilance center. Most Thai patients were willing to participate in reporting of adverse drug reactions. However, they did not know the channel of reporting (55).

**Pharmacovigilance methods**

**Passive surveillance**

Basically, spontaneous reporting system is a main method to collect adverse drug reactions. This was initiated in the 1960s because of the thalidomide disaster. Currently, it is well-established throughout developed countries and in several developing countries. The examples of the spontaneous reporting system were Yellow scheme card in the United Kingdom in 1964, Blue card in Australia in 1964, Japan in 1967, and MedWatch in the United States in 1969 (56). In Thailand, passive surveillance was started in 1983. Passive surveillance is normally managed by the central or regional organizations. Reports are voluntarily submitted by healthcare professionals and data is entered into database that is regularly screened for signals. Previously, the scheme used paper documents for reporting. Presently, electronic reporting is increasingly available. Report online was initiated in the United States, the United Kingdom, Japan

and Thailand in 1996, 2002, 2003 and 2010, respectively. Moreover, a yellow scheme card smartphone application was introduced in the United Kingdom in 2015 to support patients and healthcare professionals to report adverse drug reactions (57).

Most countries receive all reports in various routes including hard copy form, telephone or electronic submission. International medical terminology dictionaries are used for coding adverse drug reactions. Particularly, the WHO adverse reaction terminology (WHO-ART) or the medical dictionary for regulatory activities (MedDRA) are used. Additionally, information for the reports including patients' detail, time to onset of adverse drug reactions, severity of the action and outcome of the patients are gathered into the database. The feedback to reporters is given through acknowledgement (39). The strengths of spontaneous reporting system include simplicity, cover all medicines, continual monitoring throughout life cycle of a medicine, and detect signal of new, rare or serious adverse drug reactions. However, the weaknesses of this method are under-reporting and incomplete information of reports (58). Additionally, it cannot be used to calculate incidence rates.



**Active surveillance**

Active surveillance is designed to intensively monitor new drugs. These active surveillance systems mostly employ electronic medical records and claims database. For instances; the Canadian network for observational drug effect studies (CNODES) and the vaccine and immunization surveillance in Ontario (VISION); the US FDA sentinel initiative and vaccine safety datalink (VSD); the European exploring and

understanding adverse drug reactions (EU-ADR) and the vaccine adverse event surveillance and communication (VAESCO); the Shanghai drug monitoring and evaluation system (SDMES), the Asian pharmacoepidemiology network (AsPEN) (29), and the prescription event monitoring (PEM) in New Zealand, the United Kingdom, and Japan (9, 10). Additionally, stimulated reporting is used such as in early post-marketing phase vigilance (EPPV) in Japan and safety monitoring program in Thailand. This method has additional activities to enhance the reporting after new drugs are launched into the market. (32, 59).

**Proactive surveillance**

Risk management plan (RMP) is a proactive systematic approach by rapid identifying, minimizing and preventing adverse events of new drugs. International conference on harmonization (ICH) has launched RMP since November 2004. It is necessary to submit at the approval time and is amended throughout the life cycle of drugs by pharmaceutical companies (11). ICH possesses the responsibility to coordinate between pharmaceutical companies and regulatory authorities in order to discuss the registration of medicinal products for human use. The RMP was adopted by the three main ICH founding members including Europe, the United States, and Japan in 2005, 2007 and 2013, respectively (12, 13). Thailand has announced RMP for new biologic products, biosimilars, botulinum toxin and epoetin since 2017 (22).



The purposes of RMP are to explain what is recognized and

unrecognized about the safety profile of drugs, to plan how to further identify the safety profile of the drugs and to put tools in place in order to protect or decrease risks associated with drugs. The three major issues of RMP comprise the safety specification, the pharmacovigilance plan and the risk minimization plan (14, 15).

**The core structure of risk management plan**

**Safety specification** includes what is known and not known about drug safety. There are three types of safety specification characterized as follows.

- Important identified risk is defined as adverse effects observed in clinical trials or epidemiological studies. There is determination of causal relationship. In addition, it is a significant adverse drug reaction.

- Important potential risk is defined as adverse effects observed only in pre-clinical trials. There is a low incidence rate and without a causal relationship in clinical trials.



- Important missing information is defined as no available information of product safety at the time of authorization. Some populations are excluded from the trials such as pediatric, elderly or pregnancy.

**Pharmacovigilance plan** is the activity of gathering data after the products have been launched into the market. It comprises routine and additional pharmacovigilance activities.

- Routine pharmacovigilance activity is spontaneous reporting

system. It is the most common means used in routine pharmacovigilance to detect adverse drug reactions by voluntary reporting from health care professionals and patients.

- Additional pharmacovigilance activities are designed to monitor safety such as early post marketing phase vigilance (EPPV), prescription event monitoring, observational studies, and registries. Particularly, Japan initiated EPPV which was a unique regulatory requirement in October 2001. Medical representatives must provide information to healthcare professionals 2 weeks before new drugs delivery and remind every 2 weeks in the first 2 months and following once a month until 6 months have been completed. The number of ADR reports after implementing EPPV on 22 new drugs launched between October 2001 and October 2002 was higher than those before implementing EPPV on 30 new drugs approved between April 2000 and March 2001 (60). This was concordant with a study in 2013 that EPPV was positively related to the number of ADR reports of new drugs (61). In addition, the proportion of ADR reports to pharmaceutical companies was higher during EPPV period (0-6 months) than those in the post EPPV period (7-12 months) (62).



**Risk minimization plan** consists of routine and additional risk minimization activities.

- Routine risk minimization activities are the precaution and contraindication information of drugs contained in the patient leaflet and the summary of product characteristics in order to mitigate their potential adverse events.

- Additional risk minimization activities are the intervention performed to reduce serious risks and considered to be in-adequately managed by routine risk minimization activities. Additional risk minimization activities included conducting educational session or training course for healthcare professionals and patients. In addition, the activities that are beneficial to control the drug usage include restricted medical prescription, registration of physicians who can prescribe the drugs and patient registries. Furthermore, it requires the provision of drug guide for physicians, guide of dispensing for pharmacists and patient brochures. In the United Kingdom, additional risk minimization activities are frequently used for biological products compared to chemical products. The most basic types of additional risk minimization activities are educational materials for healthcare professionals. The second most common activity is educational materials for patients, followed by healthcare professionals training and registry (63). Furthermore, the evaluation of the effectiveness of additional risk minimization activities was requested by EMA, according to systematic review from 23 studies. Overall, most additional risk minimization activities reached healthcare professionals (69.6%). In addition, healthcare professional's knowledge about safety concerns was generally good (>60.0%). Most new drugs which needed additional risk minimization activities were antineoplastic and immunomodulating agents (41.4%) (64).



**The perception of RMP**

According to EMA experiences in RMP, the positive impact and

negative impact of EU-RMP were expressed by 4 EMA and national regulatory authorities, 5 well-known pharmaceutical companies and other 8 pharmaceutical companies. Both regulatory authorities and drug companies (88%) agreed that positive impact of EU-RMP was a good tool to support more structured thinking regarding a medicinal product's safety profile. In addition, half of regulatory authorities mentioned that EU-RMP was the good instrument used to communicate between regulatory authorities and drug companies. On the other hand, 65% of key informants commented that the negative impact was that additional resources including time and manpower were needed for preparing, reviewing and implementing EU-RMP. All regulatory authorities commented that it took time to review several EU-RMPs.

For provision of EU-RMP document, most regulatory authorities (75%) and drug companies (70%) appreciated that the EU-RMP template was appropriately good. However, approximately half of drug companies were dissatisfied that complex detail needed to be fill in. Other obstacles associated with EU-RMP were mentioned by regulatory authorities. For example, safety specification was occasionally incomplete. Furthermore, risk minimization activities were addressed in insufficient details. The absent issues were pharmacovigilance activities and the evaluation of the effectiveness of measures.

For risk minimization activities, regulatory authorities' perspective (25%) expressed that some drug companies exploited educational materials as the commercial tools to promote their products. Actually, risk minimization activities

should be provided for safety purposes. Additionally, regulatory authorities (75%) commented that most pharmaceutical companies did not evaluate the effectiveness of risk minimization activities well enough (65).

**Development safety update report (DSUR)**

DSUR is the periodic reporting of new drugs under investigation. The EU and US followed the ICH E2F guideline on development safety update report which has to be annually submitted to regulatory authorities. The contents of DSUR consist of the introduction, the worldwide marketing approval status, the actions taken in the reporting period for safety reasons, the changes to reference safety information, the inventory of clinical trials ongoing and completed during the reporting period, the estimated cumulative exposure, the data in line listings and summary tabulations, the significant findings from clinical trials during the reporting period, the safety findings from non-interventional studies, the other clinical trial/study safety information, the non-clinical data, the literature overall safety assessment (evaluation of the risks, benefit-risk considerations), the summary of important risks and the conclusions (66).



**Periodic safety update report (PSUR) or Periodic benefit-risk evaluation report (PBRER)**

PSUR was initiated by ICH in 1996 focusing on safety (ICH-E2C-R1). The new version was updated in 2012 as PBRER (ICH-E2C-R2) including the new issue as benefit information. The purpose of PBRER is to address a concise, comprehensive and critical evaluation of new risks and benefits balance. The contents in PBRER are

significantly imperative because this information contributes to support the committee to make decision for regulatory action taken including label change, restricted use, maintain, or revoke a marketing license.

The contents consist of the introduction (product information), the worldwide marketing authorization approval status, the action taken for safety concern, the change to reference information, the estimated exposure, the data in summary tabulations, the summary of significant findings from clinical trials during the reporting period, the findings from non-interventional studies, the information from other clinical trials and sources, the non-clinical data, the literature, overview of signal, the signal and risk evaluation, the benefit evaluation, and the integrated benefit-risk analysis for approved indication and conclusion (67).

Integrated benefit-risk analysis for approved indication comprises benefit-risk context (medical need and important alternatives) and benefit-risk analysis evaluation. The qualitative method assisting regulatory authorities and pharmaceutical companies to assess benefit-risk balance is framework with structured approach. The main components of the framework are decision context including key benefits (e.g. improve survival and increase quality of life) and key risks (e.g. important identified risks, important potential risks and important missing information), strengths, weaknesses and uncertainty of the evidence, risk management and overall benefits-risks conclusion (68).

**Safety monitoring program (SMP) in Thailand**

Pharmacovigilance system of new drugs in Thailand was safety monitoring program. SMP was the stimulated reporting surveillance that was established in 1991. It was the specific regulation directly related to new drug safety activities. The purposes of this system are to confirm new drug safety including chemical products and biologic products among Thai patients, to generate earlier safety signals before granting unconditional approval, for rigorous use of new drugs and to encourage healthcare professionals to have more concern on the safety of new drugs. New drugs include new chemical entities, new indications, new combinations, new biologic products, new delivery systems, new route of administrations, new dosage forms and new strengths.

**SMP guideline**

According to SMP guideline, the SMP products are marked with text "must monitor" within the red triangle symbol and labeled "NC" (new drug with condition) or NBC (new biologic product with condition) in order to represent conditional approval. Under the SMP, all new drugs which receive marketing approval from medicine regulatory division can be prescribed only in hospitals or healthcare facilities and cannot be distributed in the community pharmacies. New drugs must be monitored by specific stakeholders including physicians, pharmacists, nurses, and the marketing authorization holders.

New SMP regulation has been introduced since 2017. The reasons for modifying SMP guideline was that there was under-reporting. Particularly, high risk products

lacked information from clinical trial phase 3 at the time of authorization. Therefore, Thai FDA amended the SMP guideline considering about their risks. The concept was that new drugs including chemical medicines and biologic products are monitored depending on their risk. The new issues in new SMP guideline included risk-based approach, contact person for pharmacovigilance, early informing and reminding of information for new drugs with SMP and provision lists of important ADR (69). New drugs with SMP risk level 1 are new drugs approved with clinical trial phase 2, required to conduct active surveillance for all cases during every visit at least two years. New drugs with SMP risk level 2 are new chemical entities, new indications, new combinations and new biologic products which need intensified reporting for 2 years. New drugs with SMP risk level 3 are new route of administrations, new dosage forms, new delivery systems and new strengths which require intensified reporting for 1 year (32).



The marketing authorization holders must appoint the contact person for pharmacovigilance that has responsibility to gather and transfer safety report to Thai FDA. In addition, the qualified staff should have a certificate to ensure that they possess knowledge and training in the area of pharmacovigilance. Pharmaceutical companies have to coordinate with healthcare professionals in order to provide new drug safety information within 1 month before drug delivery. In addition, reminding is performed every 2 months during the first 6 months after launching new drugs into market (32).

All adverse drug reactions of new drugs under SMP are required to report to the health product vigilance center. The reporting time frame of ADRs during safety monitoring program which depends on the severity of ADRs is arranged; (1) the pharmaceutical companies must immediately report ADRs leading to death within 1 day via fax and e-mail, and then send completed document after first acknowledgement within 7 days; (2) serious ADRs should be informed within 15 days; and (3) non-serious ADRs should be reported within 2 months. Serious ADRs are classified as ADRs that cause persistent or significant disability and congenital, as well as prolonged existing hospitalization, life-threatening, and death (32).

In addition, the marketing authorization holders must submit report of safety summary every 4 months. By the end of 2 years safety monitoring program, pharmaceutical companies need to submit the comprehensive summary to Thai FDA within 3 months. These include addressing drug consumption, and detail of drug use from foreign countries. If these reports are not submitted, new drugs cannot be allowed to receive unconditional status. If the efficacy outweighs risk, new drugs will receive unconditional which will be labelled “N” or “ NB” (32).



**Pharmacovigilance assessment framework and indicators**

**Framework for assessment of the system**

Donabedian framework is a conceptual model that contributes the framework for evaluating quality of healthcare and assessing health service. It was developed in the 1960s by Avedis Donabedian who works as a physician and a

researcher at the University of Michigan. This model encompasses three dimensions including structure, process and outcome. The framework is flexible to apply in various healthcare setting (70, 71).

Structure comprises the factors that influence healthcare system. This contains operational unit, human resources, equipment, finance, staff training, and information management system. Structure is usually convenient to observe and measure.

Process composes all activities that occur. These are classified into action and interpersonal processes. First, action processes are associated with activities mainly concentrated on how care is operated. Second, interpersonal processes emphasize on the cooperation among healthcare professionals or between organizations.

Outcome includes all effects of process and structure elements on the alteration in patient or populations' status that can be categorized as behavior, knowledge, satisfaction or quality of life.



**Pharmacovigilance indicators**

The indicators are employed to measure pharmacovigilance system. They can identify the strengths and weaknesses of all components of the system including structure, process and outcome. In addition, they provide the information about the achievement of the program. The pharmacovigilance indicators are used to evaluate system at national level, hospital level and pharmaceutical company level.

The most two common pharmacovigilance indicators which are used include indicators-based pharmacovigilance assessment tool (IPAT) and the WHO indicators (33, 72).

**Indicators-based pharmacovigilance assessment tool (IPAT)**

The indicator-based pharmacovigilance assessment tool (IPAT) was developed in 2009 by management sciences for health's strengthening pharmaceutical systems (MSH/SPS) program of the U.S. agency for international development (USAID). The researchers reviewed the literature regarding the performance indicators of pharmacovigilance. Three rounds of Delphi technique were used to develop the indicators. The criteria to select the candidate indicators included objectivity, relevance, measurability, reliability, validity, and practicability. IPAT comprises 26 main indicators (12 main structure indicators, 11 main process indicators, 3 main outcome indicators) and 17 complementary indicators (3 complementary structure indicators, 7 complementary process indicator, 7 complementary outcome indicators). These indicators are aligned into pharmacovigilance components including (1) structure indicators; policy, law, regulation and stakeholders, (2) process indicators; signal detection and signal assessment (3) outcome indicators; risk management and risk communication (72). Country groups such as Sub-Saharan African countries and five Asian countries use these indicators to evaluate their system (24, 25). Additionally, individual countries such as Rwanda, Ghana, Ukraine, Burkina Faso and Benin also employ these indicators as well (73-77).

**WHO pharmacovigilance indicators**

A working group that is responsible for developing pharmacovigilance indicators includes the representative from the national pharmacovigilance centers that participates in the WHO program for international drug monitoring, the advisory committee on safety of medicinal products (ACSoMP) and staff from Uppsala monitoring center. WHO pharmacovigilance indicators were first developed in 2007 at a meeting of pharmacovigilance consultants performed in Accra, Ghana. Furthermore, these indicators were discussed and reviewed at a national meeting group in Accra, Ghana, in 2008 and then in Maputo, Mozambique in 2009. The characteristics of the indicators are simple to understand, easy to measure and interpret, independent of investigators, sensitive to detect problems, and applicable to any organization engaged in pharmacovigilance. The set of core and complementary indicators were validated by ACSoMP in 2011, 2012 and finally in 2013. Pharmacovigilance indicators comprise 27 main pharmacovigilance indicators including 10 structural, 9 process and 8 outcome indicators. In addition, there are 36 complementary indicators (11 complementary structure indicators, 13 complementary process indicators, 12 complementary outcome indicators). Individual indicators comprise definition, description, sources and methods of data collection and indicator calculation. WHO pharmacovigilance indicators were formally launched in 2015 (33). The country group that use these indicators to assess their pharmacovigilance system are in the Asia-Pacific Economic

Cooperation (APEC) (26). Nigeria also employs these indicators (78). The similarities and differences between IPAT indicators and WHO indicators are illustrated in table 1.

**Table 1** Comparison of similarities and differences between IPAT indicators and WHO indicators

| **Core structure indicators** | **IPAT indicators** | **WHO indicators** |
|---|---|---|
| The existence of pharmacovigilance center | **√** | **√** |
| Pharmacovigilance center has a clear structure, responsibilities and roles | **√** | x |
| The existence of policy or legislation for pharmacovigilance | **√** | **√** |
| The existence of specific legal for pharmacovigilance | **√** | x |
| The existence of a medicine regulatory agency | x | **√** |
| The existence of human resources | **√** | **√** |
| The existence of financial provision | **√** | **√** |
| The existence of ADR reporting form | x | **√** |
| The existence of ADR bulletin | **√** | **√** |
| The existence of advisory committee | **√** | **√** |
| The procedure in place for collecting, analyzing and recording of ADR reports | x | **√** |
| The national pharmacovigilance curriculum for the health care professionals | x | **√** |
| The drug information service center which answers on ADRs and drug safety questions | **√** | x |
| The existence of updated pharmacovigilance guidelines within the previous five years | **√** | x |
| The existence of standard operating procedures (SOPs) of medicine use for patient safety | **√** | x |
| The existence of communication technology to provision of drug information and access to safety reporting | **√** | x |

| **Complementary structure indicators** | **IPAT indicators** | **WHO indicators** |
|---|---|---|
| The national pharmacovigilance center participates as the full or the associate member of the WHO collaborating center for international drug monitoring | **√** | x |
| Legislation requires drug companies to mandatorily report all serious ADRs to the national pharmacovigilance center | **√** | x |
| Legislation requires drug companies to conduct post-marketing surveillance | **√** | x |
| The existence of requirements commanding drug companies to submit periodic safety update reports | x | **√** |
| The existence of computers for pharmacovigilance activities | x | **√** |
| The existence of information sources on prescription of drugs and consumptions | x | **√** |
| The existence of communication facilities in the national pharmacovigilance center | x | **√** |
| The existence of additional references or the library for drug safety data | x | **√** |
| The existence of the computerized ADR report system | x | **√** |
| The existence of the program for monitoring the quality of medicinal products | x | **√** |
| The existence of the essential drugs list | x | **√** |
| The existence of pharmacovigilance data when preparing the major standard treatment guideline | x | **√** |
| The national pharmacovigilance center provides training sessions for public and healthcare professionals | x | **√** |
| The existence of web-based pharmacovigilance training instruments for public and healthcare professionals | x | **√** |

| **Core process indicators** | **IPAT indicators** | **WHO indicators** |
|---|---|---|
| Strategy or platform for collaboration of pharmacovigilance activities across all stakeholders | **√** | x |
| The system has the collation of drugs safety data from all sources to the database at the national pharmacovigilance center | **√** | x |
| The existence of the database for pharmacovigilance activities | **√** | x |
| The existence of the suspected ADRs reporting form | **√** | x |
| The existence of the suspected product quality issues reporting form | **√** | x |
| The existence of the suspected medication errors reporting form | **√** | x |
| The existence of the suspected treatment failure reporting form | **√** | x |
| The number of ADR reports obtained in the previous year | **√** | **√** |
| The number of active surveillances conducted in the previous five years | **√** | **√** |
| Percentage of the patients who have adverse drug events in public health programs in the previous year | **√** | x |
| Percentage of the patients who receive new treatment due to ADRs in public health program in the previous year | **√** | x |
| The number of current reports in the local database or regional or national | x | **√** |
| A percentage of the annual reports acknowledged or feedback | x | **√** |
| A percentage of the reports aim at causality assessment in the previous year | x | **√** |
| A percentage of the annual reports completed and submitted to WHO database | x | **√** |
| A percentage of the therapeutic ineffectiveness reports obtained in the last year | x | **√** |
| A percentage of the medication errors' report obtained in the last year | x | **√** |
| A percentage of the pharmaceutical manufactures which have a pharmacovigilance system | x | **√** |

| Complementary process indicators | IPAT indicators | WHO indicators |
|---|---|---|
| Percentage of the main reference materials existing in the national pharmacovigilance center | √ | x |
| Percentage of the main pharmacovigilance topics presented in the training courses | √ | √ |
| The number of healthcare professionals trained on pharmacovigilance and drug safety in the previous year | √ | √ |
| The number of drug use reviews processed in the previous year | √ | x |
| Medicinal products quality was surveyed in the previous five year | √ | x |
| The quantification of incidence of medication errors in the previous year | √ | x |
| Percentage of patients who have severe unexpected adverse events in public health programs in the previous year | √ | x |
| Percentage of hospitals which submit more than 10 reports to the national pharmacovigilance center | x | √ |
| Percentage of the ADR reports sent in the last year by the various stakeholders including physicians, dentists, pharmacists, nurses, general public and manufactures | x | √ |
| The total number of ADR reports per million population per year | x | √ |
| The average number of ADR reports per number of health professionals per year including physicians, dentists, pharmacists and nurses | x | √ |
| Percentage of healthcare professionals understand and aware of ADRs per hospital | x | √ |
| Percentage of the patients who leave a hospital aware of ADR | x | √ |
| The total number of specific medicinal products reporting per volume of sales from the pharmaceutical manufactures | x | √ |
| The number of registered medicinal products with the risk management plan in the pharmaceutical manufactures | x | √ |

| **Complementary process indicators** | **IPAT indicators** | **WHO indicators** |
|---|---|---|
| Percentage of pharmaceutical manufactures who submit periodic safety update reports to the drug regulatory agency | x | **√** |
| Number of medicinal products voluntarily withdrawn by pharmaceutical manufactures due to safety concerns in the last year | x | **√** |
| Number of ADR reports from individual pharmaceutical manufactures received by the national pharmacovigilance center in the last year | x | **√** |
| **Core outcome indicators** | **IPAT indicators** | **WHO indicators** |
| Number of regulatory actions | x | **√** |
| Number of signals identified in the last 5 years | x | **√** |
| Number of drugs related hospital admissions per 1000 admissions | x | **√** |
| Number of drugs related deaths per 1000 persons per year | x | **√** |
| Number of drugs related deaths per 100,000 persons in the population | x | **√** |
| The average cost (US$) of treatment of drugs related sickness | x | **√** |
| The average period of drugs related expansion of hospital stays | x | **√** |
| The average cost (US$) of medicine-related hospitalization | x | **√** |
| The average time lag between detection of signal of a suspected ADR or important drugs safety issue and dissemination to health care professionals and the public | **√** | x |
| A percentage of the drug and therapeutics committees that have processed pharmacovigilance activities in the previous year | **√** | x |
| A percentage of medicinal products passing product quality tests in the previous year | **√** | x |
| **Complementary outcome indicators** | **IPAT indicators** | **WHO indicators** |
| The existence of risk management plans that are aimed at high-risk medicinal products | **√** | x |
| Pharmaceutical inspection | **√** | x |

| **Complementary outcome indicators** | **IPAT indicators** | **WHO indicators** |
|---|---|---|
| Number of data safety requests in the previous year | **√** | x |
| Percentage of medicinal products safety bulletin published in the previous year | **√** | x |
| Number of drug safety issues identified from international sources | **√** | x |
| Number of “Dear healthcare professional” letters or additional safety alerts disseminated in the previous year | **√** | x |
| Number of community or public education sessions associated with medicinal products safety processed in the previous year | **√** | x |
| Percentage of protectable ADRs reported out of the total number of ADRs reported in the last year | x | **√** |
| Number of medicinal products associated with congenital malformations per 100,000 births | x | **√** |
| Number of medicinal products identified to be probably related to congenital malformations in the previous 5 years | x | **√** |
| Percentage of medicinal products that are counterfeit or substandard in the pharmaceutical market | x | **√** |
| Number of patients who have the medication errors in the hospital per 1000 admissions in the last year | x | **√** |
| Average schooldays or workdays lost because of drug related problems | x | **√** |
| Cost saving of pharmacovigilance activities | x | **√** |
| Health financial impact of pharmacovigilance activities | x | **√** |
| Average number of medicinal products per prescription | x | **√** |
| The percentage of prescriptions with medicines overdose | x | **√** |
| The percentage of prescription with the potential drug interaction | x | **√** |
| The percentage of patients provided information on potential ADRs and how to use the medicines | x | **√** |

**Thailand safety monitoring program indicators**

Thailand safety monitoring program indicators were constructed by using three-round modified Delphi method. Data collection included face to face semi-structured interviews, mailed questionnaire, and telephone. The 32 participants associated with the SMP were invited by face-to-face contact or telephone to enroll in an expert group. The first round was performed to survey with the open-ended questions requesting what the indicators are in the SMP. The first round, the second round and the third round provided 71 indicators, 40 indicators, and 36 indicators, respectively. Then, the indicators were finally reclassified by the similar issues into 19 indicators. Five-point Likert rating scale was employed to score suitability of individual indicator from "most suitable" to "least suitable"(17). Thailand safety monitoring program indicators are presented in table 2.

**Table 2** Thailand safety monitoring program indicators

| **Structure indicators** | |
|---|---|
| Policy, law, regulation and guideline | -The existence of new drug safety monitoring system at national level<br>-The existence of new drug safety monitoring guidelines in FDA |
| Institution | -The existence of new drug safety monitoring system at hospital level<br>-The existence of new drug safety monitoring system in drug companies |

| | |
|---|---|
| Staff | - Appointed staff for safety monitoring activities in companies<br>- Experienced external professionals in new drug<br>- Experienced staff in pharmaceutical manufactures |
| Information database | - National database that links ADRs of new drug to the WHO Vigibase<br>- Information database of new drugs includes regulatory measures in foreign countries, indication, adverse drug reactions, contraindication, and drug interaction |
| **Process indicators** | |
| Assessment process for new drugs registration with SMP | -The significant criteria for registration of new drugs to the SMP |
| Management of ADRs | -The accuracy of ADR reporting from healthcare professionals<br>-The performing of ADR collecting from drug companies<br>-ADR assessment process |
| Assessment process for removing new drugs from SMP | -The exact criteria for removing new drug from the SMP<br>-The transparence process in the SMP |
| **Outcome indicators** | -The incidence of adverse drug reactions<br>-The foreign case report of adverse drug reactions<br>-The effectiveness of Thailand adverse drug reaction reporting<br>-Identification of serious ADR |

**Performance of pharmacovigilance system across the globe**

Five Asian countries including Bangladesh, Cambodia, Nepal, Philippines and Thailand and 46 African countries were evaluated for pharmacovigilance system at national level, pharmaceutical company level and hospital levels while 15 countries of Asia Pacific Economic Cooperation (APEC) including Australia, Brunei, Chile, Indonesia, Japan, Korea, Malaysia, Mexico, Papua New Guinea, Peru, Philippines, Singapore, Taiwan, Thailand and the United States were assessed only national level. IPAT indicators and WHO indicators mentioned above were employed to assess pharmacovigilance system in these groups of countries.

National level

Under-reporting was found in 4 Asian countries except for Thailand. Thailand collected ADR more than 200 reports per million population. Furthermore, only Thailand performed active surveillance. Medicine safety bulletins were regularly published in Nepal and Thailand (25). Of the 46 countries in African countries, 74% had spontaneous reporting system. Only 2 countries gathered ADRs more than 100 reports per million population in 2010 and most of the countries had ADRs less than 20 reports per million population per year. Only 48 % conducted active surveillance in the last 5 years. Medicine safety newsletters were issued in 20%. Risk management activities were not established in African countries (24). According to the evaluation, the significant problem was under-reporting in most Asian countries and African countries. All 15 countries (APEC) had PV regulations and 12 countries required RMP. Nine countries

carried out active surveillance on top of spontaneous reporting system (26). Eight countries of the Association of Southeast Asian Nation (ASEAN) including Cambodia, Indonesia, Loas, Malaysia, Philippines, Singapore, Thailand and Vietnam responded to the survey. Four countries including Indonesia, Malaysia, Singapore and Thailand attained all elements of WHO minimum requirement to process PV system. The other four countries had obscure risk communication (23).

Pharmaceutical company level

In 5 Asian countries, 38 pharmaceutical industries consisted of the generic manufacturers, the local innovators, the multinational generic and the multinational innovators. Only 23 of those 38 pharmaceutical companies had a standard operating procedure, only 16 pharmaceutical companies collected and submitted adverse drug reaction reports to the national pharmacovigilance center and only 15 pharmaceutical companies conducted active surveillance activities. In Sub-Saharan Africa, 21 pharmaceutical companies in 7 countries consisted of 10 multinational innovators, 4 multinational generic and 7 local owned companies. Only 3 drug companies conducted the post-marketing surveillance, 5 drug companies had the ADR reporting forms or the standard operating procedure, and 8 pharmaceutical companies had a department or staff responsible for pharmacovigilance activities. It indicated that the pharmaceutical companies' compliance in pharmacovigilance activities was partial because of the ineffective enforcement of national regulations in developing countries.

Hospital level

Less than half of 86 hospitals in 5 Asian countries had availability of ADR reporting form. A quarter of hospitals in Nepal, Thailand and Philippines received medicines safety bulletins from their national PV center. According to studies in EU, more than 90% of 1766 general practitioners in 26 EU countries received direct healthcare professional communication from national regulatory authorities. These general practitioners received them via an electronic channel rather than a hard copy (40). In addition, approximately 92% of 3822 healthcare professionals from 9 EU countries including Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden and the UK were familiar with direct healthcare professional communication. However, the cardiologists had less awareness of safety concerns related to non-cardiology medicines, although cardiovascular safety was found in these medicines. This implied that it needed extra strategies to disseminate safety issues that were outside their specialist area (79).



**Performance of pharmacovigilance system in Thailand**

Thailand established adverse drug reaction monitoring center (ADRMC) in 1983 which was controlled by the Thai Food and Drug Administration. The name of this center was modified to adverse product reaction monitoring center (APRMC) in 1997 in order to cover all products rather than medicinal products, and then name was changed to health product vigilance center (HPVC) in 2008. Thailand pharmacovigilance center has a well-organized structure, sufficient funding, qualified staff and good

information technology. The HPVC had 9 full-time pharmacy staff. Head of HPVC had obligation to supervise the center's functions including risk collection, risk assessment, risk management and risk communication. The 8 pharmacists were rotated into each function every two years. HPVC had enough manpower. However, they mentioned that they lacked knowledge in pharmacoepidemiology to support their task (16).

**The processes of pharmacovigilance system in Thailand**

Risk collection

Previously, the method of monitoring new drugs with SMP in drug companies and hospitals was similar to other drugs by using passive surveillance (18). The completeness of ADR reports obtained from hospitals and drug companies were measured by using the WHO-UMC's documentation grading criteria which ranged from grade 0 to grade 3. Grade 0 was the minimum requirements while a high grade reflected high quality data. As a result of analyzing data in Thai vigibase in 2012, the quality of ADR reports with grade 2 was 76.6%, followed by 20% grade 0 to grade 1 whereas only 4.1% reach grade 3 (16).



Risk assessment

Data sources

For local data sources, HPVC analyzed data in Thai vigibase every 6 months employing "Reporting Odds Ratio (ROR)". It was a disproportionality measurement to identify safety signal. HPVC staff also reviewed pharmacoepidemiology and medical pharmacological literature to complement the

domestic data sources (16). There was low number of ADR reports of new drugs with SMP for Thai population (18) .

For global data sources, HPVC staff accessed official drug regulatory authority website including EU, USA and Australia. The reasons for selecting those were that those drug regulatory authority websites were publicly accessible, information was reliable and updated. Apart from foreign drug regulatory authority websites, HPVC staff also searched additional data from WHO website as well as mass media such as BBC and CNN. HPVC staff reviewed foreign data sources every day. Then, HPVC staff supplied all data sources to the national drug advisory sub-committee to consider in order to take regulatory action (16).

Risk assessment for taking regulatory action

The national drug advisory sub-committee consisted of 3 main groups including Thai FDA staff, the experts in the areas of pharmacoepidemiology or pharmacology or medicine and public representatives. The committee meetings were normally set at least 4 times a year. However, there was no pre-set schedule. Members in the committee might be unavailable at the same time. Therefore, it was difficult to manage. Time to make decision ranged from 1 month to almost 3 years. Time to make decision was between date of signal awareness and date of decision making. Date of signal awareness was defined as the date that safety issues were identified as potential signal. Date of decision making was defined as date of the national drug advisory committee making a decision. The reasons for taking time in making decision were that

there were no prioritizing criteria for managing unexpected cases or serious cases. Furthermore, it took time for weighting benefit-risk balance. In addition, it required further studies in some cases (16).

Risk assessment for removing new drugs from SMP

Only 2 experts were employed in the evaluation for removing new drugs from SMP including 1 specialist physician in clinical study and 1 FDA officer. If the FDA officer opposed the expert's decision, the expert's opinion was only accepted. There was inadequate expertise. In addition, there were no criteria for removing new drugs from SMP. Therefore, the decision was solely based on the expert's personal experiences. From Thai FDA perspectives on SMP monitoring period, the biologic products had average time in the SMP greater than 2 years since there was complexity in evaluation of this kind of product. According to drug companies' experiences, the SMP period ranged from 6 months to 2 years depending on experts' consideration or the activeness of the FDA officers. For new chemical entity, the SMP period took more than 2 years in the SMP while the new strength or dosage form, the SMP period took less than 2 years (18).



Risk communication

Materials for risk communication include "Medical and Health product bulletin" and "Safety alerts". The bulletin was issued quarterly. For "safety alerts", emergency or serious information was immediately circulated. The information was sent to hospitals, not directly to healthcare professionals. Therefore, it could not

confirm whether individual healthcare professionals received and read the distributed information. The average lag time from the advisory drug committee's decision to communicate safety information for safety alert and periodic bulletin was 7 days and more than 1 month, respectively. Pre-specified timetable for risk communication was not established. Both the bulletin and the safety alerts were mainly disseminated in hardcopy format. Another channel of distributing safety information was HPVC website. However, it was not convenient in a user-friendly manner because it was difficult to search by key words. The HPVC did not have its own staff to supervise and develop its website. The outsourced administrator was responsible for maintaining its website. Social media should be developed to complement the traditional channels (16).

The collaboration between pre-marketing division and post-marketing division

The collaboration related to safety monitoring program (SMP)

between the medicine regulatory division and the national pharmacovigilance center was not satisfactory. The medicine regulatory division has a duty to supply SMP drug list to the national pharmacovigilance center. The national pharmacovigilance center provides safety reports to the medicine regulatory division. The coordination between two divisions was based on formal document communication. Information technology communication system and database were not yet set. Workflow of pre-marketing division and post-market division need to be developed and implemented (16). Pre-marketing commented that the 4-monthly summary of ADR of new drugs under SMP

from post-marketing division was found difficult to understand and to use for pre-marketing division (18).

# CHAPTER III

# METHODOLOGY

This study encompassed two objectives. The first objective was to review the pharmacovigilance system of new drugs in targeted countries in order to understand how those countries manage their systems in comparison to Thailand. The second objective was to assess the pharmacovigilance system of new drugs in Thailand which after 2017 had major revision implementing the risk management plan (RMP) and risk-based safety monitoring program (SMP).

**Methodology of the first objective: Review pharmacovigilance system of new drugs in targeted countries**

The study utilized systematic review to explore pharmacovigilance systems of new drugs. The methods of systematic review followed PRISMA checklists 2020. The search was conducted from the inception to January 2019 using Pub-med, Scopus and Google scholar. The inclusion criteria for articles were that articles provided information on pharmacovigilance system of new drugs, all publication years, publication types including original articles, review articles and conference articles. The exclusion criteria for articles were non-English. The keywords were used in two terms as follows; (1) pharmacovigilance terms: pharmacovigilance OR “post-marketing surveillance” OR “safety monitoring” OR “safety surveillance” OR “intensive monitoring” OR “active surveillance”; (2) new drug terms: “new drug” OR “new drugs” OR “new medicine”

OR “new medicines” OR “new chemical entity” OR “new chemical entities” OR “new active substance” OR “new active substances”.

According to systematic review from the specified database, the findings provided 11 countries with pharmacovigilance system of new drugs including 8 high income countries (Australia, Canada, Japan, the Netherlands, New Zealand, Sweden, the United Kingdom and the United States) and 3 upper-middle income countries (Brazil, China and Thailand). The issue of pharmacovigilance of new drugs may not be frequently mentioned in a research paper, but rather seen as a routine work. The scoping review strategy would then focus on searching the drug regulatory agencies’ official websites. Also, the preliminary result found that most countries extracted from systematic review were high income countries and upper-middle income countries. Thus, the study focused on high income countries and upper-middle income countries.

Google was used to search drug regulatory authority websites and Ministry of Health websites. The searching was commenced in July 2020 to August 2021. Keywords were used in term of “drug regulatory authority” OR “drug regulatory agency” OR “medicine regulatory authority” OR “medicine regulatory agency” OR “Food and Drug Administration” OR “Ministry of Health”. The lists of countries were retrieved from world bank lists of economies updated in June 2020. Then, names of countries were combined with the keywords using “AND” and filled into the search engine website. The inclusion criteria for websites were that websites provided information on pharmacovigilance system of new drugs. The exclusion criteria for websites were that

information on websites was non-English. The examples of countries and their websites were shown in table 3.

The framework was categorized into structures and processes. The specific activities of new drugs in each component were extracted. Structures consisted of guideline on pharmacovigilance system, authorized drug product database and public accessibility of ADR reports. Processes comprised risk management plan, risk collection, risk assessment, risk communication and pharmacovigilance inspection. The components of risk management plan included RMP product coverage scope, global/local RMP submission and publication of approved RMP. The components of risk collection encompassed post-authorization safety study, pre-specified monitoring period, ADR reporting channels and time to report ADR. The components of risk assessment were periodic safety update report (PSUR) submission interval, the application of risk assessment output, the publication of risk assessment report and the risk assessment committee. The components of risk communication comprised types and risk communication channels. For data synthesis, the results were presented using narrative approach that included description of the management of pharmacovigilance system of new drugs.

**Table 3** The examples of countries and their website

| Countries/ Group of countries | National FDA website |
|---|---|
| European | https://www.ema.europa.eu/en |
| The United Kingdom | https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency |
| The United States | https://www.fda.gov/drugs |
| Japan | https://www.pmda.go.jp/english/ |
| Thailand | http://www.fda.moph.go.th/ |

**Methodology of the second objective: Assessment of pharmacovigilance system of new drugs in Thailand**

The significant stakeholders were in-depth interviewed including regulatory authorities from Thai FDA, pharmacists from pharmaceutical companies and healthcare professionals from hospitals including the physicians and the pharmacists. The collection tool was semi-structured interview questionnaire. The questionnaire contained questions to investigate the participants' opinion regarding the current pharmacovigilance system of new drugs in Thailand. Purposive sampling was used to select participant. Then, snowball technique was used to approach samples. The researcher sent the letters with the specification of qualification of participants to Thai FDA, drug companies and hospitals to allow interviewing.

**Sample selection**

**Thai FDA**

The inclusion criteria for selecting regulatory authorities from Medicine Regulatory Division (pre-marketing division) included responsible pharmacists for approving, removing new drugs with SMP and reviewing RMP. The inclusion criteria for selecting regulatory authorities from Health Product Vigilance Center (HPVC, post-marketing division) included responsible pharmacists for monitoring safety of medicinal products. The experience of key informants must be more than 1 year. The sample size of pharmacists from Thai FDA was six.

**Drug companies**

The inclusion criteria for selecting drug companies were that those had launched new drugs with SMP in the multinational drug companies and the distributor drug companies. The sample size was 6 drug companies. The inclusion criteria for selecting pharmacists from drug companies included responsible pharmacist for pharmacovigilance activities. The experience of key informants must be more than 1 year. The sample size was 1 pharmacist for each drug company.



**Hospitals**

The inclusion criteria for selecting hospitals were that those prescribed new drugs with SMP in the university hospitals and tertiary hospitals. The sample size was 6 hospitals. Pharmacists and physicians were from the same hospitals. The experience of key informants must be more than 1 year.

The inclusion criteria for selecting pharmacists from hospital were responsible ADR pharmacists or DIS (drug information services) pharmacists and operational pharmacists. The reason for selecting those pharmacists was because they had responsibility in ADR collecting and ADR reporting to Thai FDA. The sample size was 2 pharmacists for each hospital.

The inclusion criteria for selecting physicians from hospital were responsible physicians for prescribing new drugs with SMP. The sample size was 2 physicians for each hospital.

**Questionnaire development**

The instrument was semi-structured interview questionnaire. The processes of questionnaire development consisted of reviewing the components of pharmacovigilance system of new drugs from Thailand RMP, SMP guideline and the components from the first objective. Then, questionnaire validity and pilot test were processed.



The framework of assessment of pharmacovigilance system of new drugs in Thailand was categorized into structures, processes and outputs. RMP structure was RMP guideline. RMP processes consisted of RMP submission, RMP update and inspection. SMP structures included SMP guideline, SMP protocol and national database of approved drugs. SMP processes comprised the distribution of safety information, method of monitoring in drug companies and hospitals, ADR reporting to Thai FDA, risk assessment and risk communication. Outputs included number of ADR

reports of new drugs with SMP, number of signal detection of new drugs with SMP, regulatory action taken of new drugs with SMP and actual monitoring of new drugs with SMP. Then, the questions were established for each component. The semi-structured questionnaire was addressed in Appendix A.

The semi-structured questions could be applied with each of three stakeholders. The elaboration for this was that there was the coordination among all three stakeholders to reach the purpose of RMP and SMP. All three stakeholders answered the same questions from their perspective. In addition, some specific questions were required for each of three stakeholders according to their responsibilities relating to RMP and SMP.

**Questionnaire validity**

All the questions were considered for content validity by three experts in the academic field. The experts assessed whether the contents of questions followed the objective of RMP and SMP.



**Pilot test**

The pilot study to test the questionnaire were conducted on relevant stakeholders including regulatory authorities from Thai FDA, pharmacists from pharmaceutical companies, physicians and pharmacists from hospitals.

**Data collection**

Face-to-face semi-structured interview were performed with key informants who consented to participate in the study. The key informants were asked for the permission of taking handwritten notes and audio recording at the same time. They were requested to answer and express their opinion to the questions associated with pharmacovigilance system of new drugs. The information provided by the participants was kept strictly confidential. The recording files were coded with identification number of the key informants and were destroyed within 1 year after the completing of the study. The researcher continued sampling and analyzing data until saturation. In other words, no new data appeared.

The audio recording was transcribed verbatim before initiating of data analysis. Then, the researcher listened to the recording and read the transcription simultaneously and corrected the errors of spelling. Coding was exploited to the identification of topics, similarities and differences revealed through the key informants' narrative.



Trustworthiness was evaluated to prove validity and reliability of information by clarifying what the key informants provided by asking them what they meant or by describing to them what the researcher heard during interview. Triangulation also was used to confirm the validity of the information from key informants.

**Data analysis**

Codes from all transcriptions were merged into a theme framework in order to present the results of qualitative research in meaningful and obvious way.

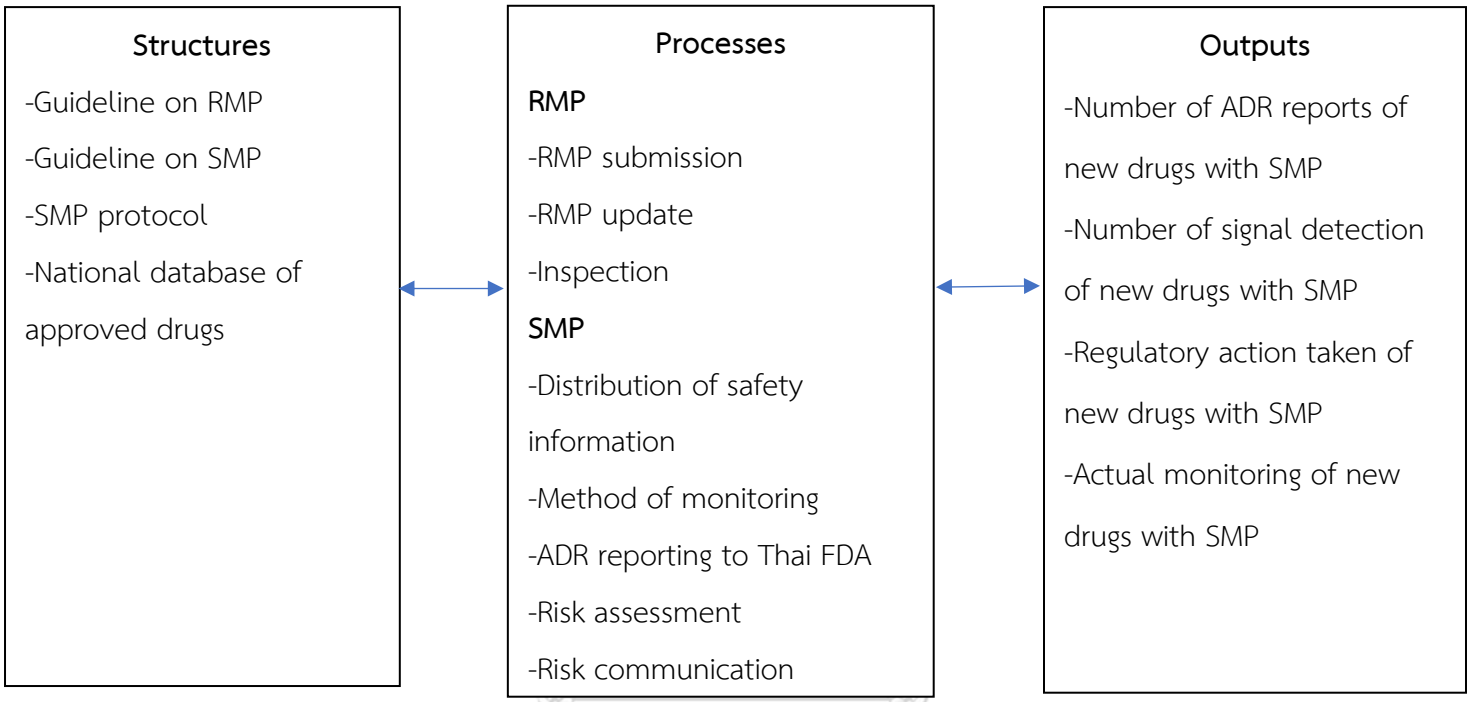


**Figure 1 Pharmacovigilance assessment framework**



**The description of pharmacovigilance assessment framework**

**RMP Guideline**

The purpose of RMP guideline was to facilitate relevant stakeholders to implement RMP activities in real practice. RMP guideline was detailed in term of awareness of RMP guideline, understanding of RMP guideline (clarity of RMP guideline and RMP product coverage scope).

**RMP submission**

The purpose of RMP submission was to ensure that drug companies addressed the completeness of safety specification, appropriate risk minimization activities and appropriate pharmacovigilance activities.

**RMP update**

The purpose of RMP update was to add new safety in RMP. The compliance of RMP update and awareness of the importance of RMP update were detailed.

**Inspection**

The purpose of inspection was to evaluate whether drug companies complied with pharmacovigilance obligation.

**SMP guideline**

The purpose of SMP guideline was to facilitate relevant stakeholders to implement activities in real practice. Awareness of SMP guideline, understanding of SMP guideline (clarity of SMP guideline and opinion on SMP risk-based approach) were explained.



**SMP protocol**

The purpose of SMP protocol was to assist relevant stakeholders to carry out risk minimization activities and pharmacovigilance activities.

**National database of approved drugs**

The purpose of the national database of approved drugs was to facilitate relevant stakeholders to check the status of new drugs with SMP.

**Distribution of safety information**

The purpose of safety information was to inform important ADRs to relevant stakeholders to monitor. Timetable for early informing and reminding, methods of early informing and reminding, awareness of important ADRs and usability were elucidated.

**Method of monitoring**

Risk minimization activities

The purpose of risk minimization activities was to reduce and prevent serious ADRs. The components of risk minimization activities comprised compliance of pre-prescribing for new cases and routine follow-up, and compliance of ADR management and counselling.



Pharmacovigilance activities

The aim of pharmacovigilance activities was to identify ADR. New drugs with SMP risk level 1 required to conduct active vigilance for all cases at every visit. New drugs with SMP risk level 2 and risk level 3 were monitored by using intensified reporting system. The elements of pharmacovigilance activities consisted of

identifying methods, timetable to follow-up, causality assessment, types of ADR report, and number of ADR reports.

**ADR reporting**

Completeness of ADR reports

The purpose of reporting complete ADR information was to support signal detection.

Types of ADR report

The purpose of reporting all types of ADRs was to know frequency and severity in order to compare with data from clinical trial whether there was unusual frequency or unknown ADRs.

Time to report ADR

The purpose of reporting in time was to accelerate to take regulatory action.



Route of ADR reporting

The purpose of reporting with appropriate route was to send complete information into database.

**Risk assessment**

The purpose of risk assessment was to evaluate benefit-risk balance of new drugs with SMP in order to take regulatory action and remove new drugs from SMP. The components of risk assessment include PSUR, national database of ADR reports, decision on risk assessment for taking regulatory action, and decision on risk

assessment for removing new drugs from condition. PSUR and national database of ADR reports were data sources for risk assessment to take regulatory action and remove new drugs from SMP.

**Risk communication**

The purpose of risk communication was to inform new ADR to targeted healthcare professionals so that they could take action in appropriate time. Risk communication channels and timetable to communicate were described for Thai FDA newsletter and DHPC of drug companies.

# CHAPTER IV

# RESULTS

## Results of the first objective: Review pharmacovigilance system of new drugs in targeted countries

Preliminary results obtained from systematic review were presented following PRISMA flow 2020. Thirty-eight full texts of articles were included in review as show in figure 2. Pharmacovigilance system of new drugs were found in 11 countries including 8 high income countries (Australia, Canada, Japan, the Netherlands, New Zealand, Sweden, the United Kingdom and the United States) and 3 upper-middle income countries (Brazil, China and Thailand). (Appendix B). Issues of pharmacovigilance system of new drugs were not frequently mentioned in the research papers. Then, systematic review was searched from drug regulatory authority websites.

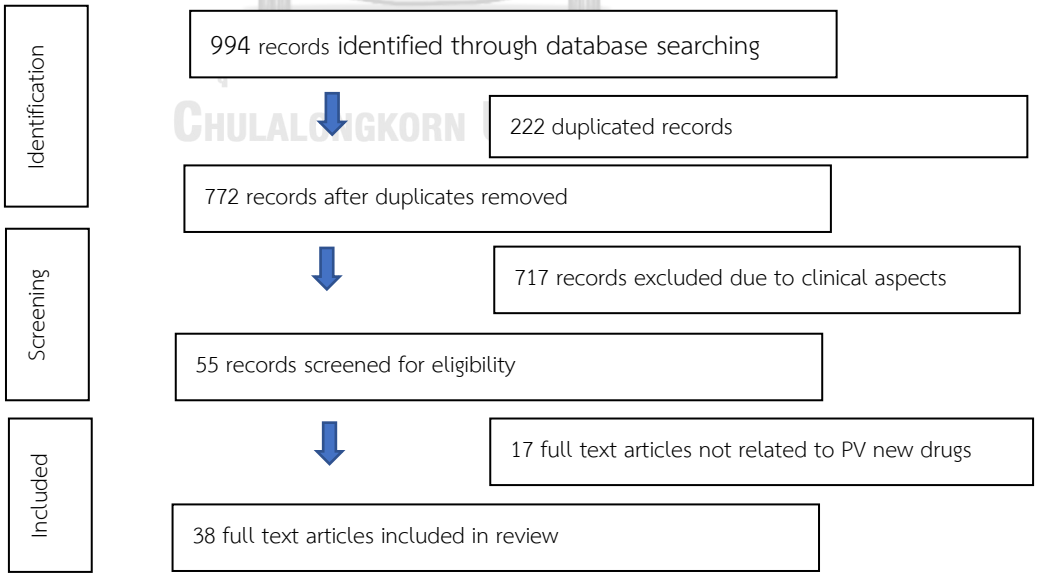


Figure 2 Systematic review search from database

Among 139 included countries, 129 countries had drug regulatory authority websites or Ministry of Health websites and 87 countries had pharmacovigilance system of new drugs. The search results were summarized in figure 3.

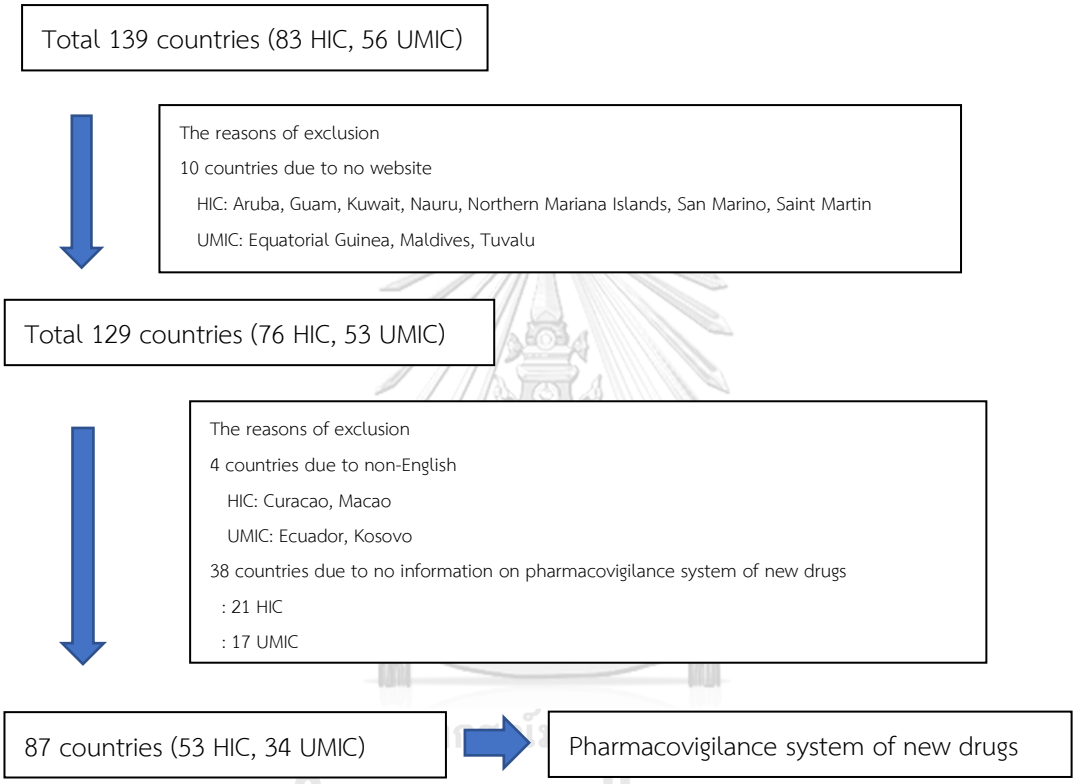


**Figure 3 Scoping review search from regulatory authority websites**

Data were extracted according to the framework. The data sources were obtained from drug regulatory authority websites and Ministry of Health websites. The links of each website were appended in Appendix C. Countries were categorized into 53 high income countries (60.92%) and 34 upper-middle income countries (39.08%). Lists of countries' abbreviation and full name were presented in table 4.

**Table 4 Countries' abbreviation and full name**

| | |
|---|---|
| **High income countries** 53 countries (60.92%) | AD-Andorra, AE-the United Arab Emirates, AT-Austria, AU-Australia, BB-Barbados, BE-Belgium, BN-Brunei Darussalam, CA-Canada, CH-Switzerland, CL-Chile, CY-Cyprus, CZ-Czech Republic, DE-Germany, DK-Denmark, EE-Estonia, ES-Spain, FI-Finland, FR-France, GR-Greece, HK-Hong Kong, HR-Croatia, HU-Hungary, IE-Ireland, IL-Israel, IS-Iceland, IT-Italy, JP-Japan, KR-Korea, LI-Liechtenstein, LT-Lithuania, LU-Luxembourg, LV-Latvia, MT-Malta, MU-Mauritius, NC-New Caledonia, NL-the Netherlands, NO-Norway, NZ-New Zealand, OM-Oman, PA-Panama, PL-Poland, PT- Portugal, RO-Romania, SA-Saudi Arabia, SE-Sweden, SG-Singapore, SK-Slovakia, SI-Slovenia, TT-Trinidad and Tobago, TW-Taiwan, UK-the United Kingdom, US-the United States, UY-Uruguay |
| **Upper middle-income countries** 34 countries (39.08%) | AL-Albania, AM-Armenia, AR-Argentina, AZ-Azerbaijan, BA-Bosnia and Herzegovina, BG-Bulgaria, BR-Brazil, BW-Botswana, BY-Belarus, BZ-Belize, CN-China, CO-Colombia, CR-Costa Rica, CU-Cuba, DO-Dominican Republic, GT-Guatemala, ID-Indonesia, IR-Iran, IQ-Iraq, JM-Jamaica, JO-Jordan, KZ-Kazakhstan, ME-Montenegro, MK-Macedonia, MX-Mexico, MY-Malaysia, NA-Namibia, PE-Peru, RS-Serbia, RU-Russia, TH-Thailand, TR-Turkey, VE-Venezuela, ZA-South Africa |

**STRUCTURES**



Structures consisted of availability of pharmacovigilance system guideline, availability of authorized drug product database and public accessibility of ADR reports.

**Availability of pharmacovigilance system guideline**

Pharmacovigilance system guidelines were available in 60 countries (68.97%). Of these, 43 countries (49.43%) mentioned the requirement of post-authorization safety study (PASS) within pre-specified monitoring period. On the

other hand, 27 countries (31.03%) did not specify guideline on pharmacovigilance system. The availability of pharmacovigilance guideline was presented in table 5. The lists of guidelines on pharmacovigilance system and update year were appended in Appendix D.

**Table 5 Availability of pharmacovigilance system guideline**

| | | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|---|
| **PV guideline** | Mention the requirement of PASS within pre-specified monitoring period for new drugs | HIC | 38/87 (43.68%) | AT, AU, BE, CA, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR HU, IS, IE, IT, JP, KR, LV, LT, LU, MT, NL, NZ, NO, PL, PT, RO, SE, SG, SI, SK, TW, UK, US |
| | | UMIC | 5/87 (5.75%) | BR, BG, CN, TH, TR |
| | Not mention the requirement of PASS for new drugs | HIC | 8/87 (9.20%) | AE, BN, HK, IL, MU, OM, PA, SA |
| | | UMIC | 9/87 (10.34%) | AM, BW, IQ, JO, MY, NA, RU, RS, ZA |
| **Total** | | | **60/87 (68.97%)** | |
| **Not specify PV guideline** | | HIC | 7/87 (8.04%) | AD, BB, CL, LI, NC, TT, UY |
| | | UMIC | 20/87 (22.99%) | AL, AR, AZ, BY, BA, BZ, ID, KZ, ME, MK, CO, CR, CU, DO, GT, JM, MX, PE, VE, IR |
| **Total** | | | **27/87 (31.03%)** | |

**Availability of authorized drug product database**

Authorized drug product databases were available in 52 countries (59.77%) whereas 35 countries (40.23%) had no authorized drug product database. Availability of authorized drug product database was illustrated in table 6. The characteristics of authorized drug product database included the specification of special contents for new drugs subject to conduct post-authorization safety studies and providing drug information. Eight countries (15.38%) addressed special contents for new drugs including new drugs symbol in 5 high income countries, type of new drugs in 2 high income countries and status of new drugs with condition in 1 upper-middle income country. Five high income countries including Belgium, Iceland, Lithuania, the Netherlands and Spain addressed inverted black triangle symbol in authorized drug product database to notify that this new drug was under extra monitoring. Two high income countries including Japan and the United States mentioned types of new drugs in authorized drug product database. One upper-middle income countries, Thailand addressed status of new drugs with wording “within SMP condition or remove from SMP”. The contents of authorized drug product database were detailed in Appendix E.



At regional level, EMA monthly updated line listing of new medicines under additional monitoring in PDF file and Excel file to present status of new medicinal products. The new medicines added to the list were shown in red front. The new medicines removed from the list were shown with a strikethrough for the

period of one month after they were excluded. The contents in file included product names, active substances, marketing authorization holders, link to product information (PIL, SPC and RMP) and date of inclusion into the lists.

Basically, the information available on authorized drug product database was product name (tradename and generic), strength, dosage form, route of administration and marketing authorization holder. Moreover, 24 countries (46.16%) provided download files for drug information including patient information leaflet, summary product characteristics or educational material. The characteristics of authorized drug product was shown in table 7.

**Table 6 Availability of authorized drug product database**

| | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| **Authorized drug product database** | HIC | 35/87 (40.23%) | AT, AU, BE, CA, CH, CZ, DK, EE, ES, FI, FR, HK, HU, HR, IS, IE, IL, IT, JP, LV, LT, MT, NL, NZ, NO, PT, RO, SA, SE, SI, SK, SG, TT, UK, US |
| | UMIC | 17/87 (19.54%) | AL, AR, AM, AZ, BG, BR, BY, CN, ID, IR, MK, MY, NA, RS, TH, VE, ZA |
| **Total** | | **52/87 (59.77%)** | |
| **No authorized drug product database** | HIC | 18/87 (20.69%) | AD, AE, BB, BN, DE, CL, CY, GR, KR, LI, LU, MU, NC, OM, PA, PL, TW, UY |
| | UMIC | 17/87 (19.54%) | BA, BW, BZ, CO, CR, CU, DO, GT, IQ, JM, JO, KZ, ME, MX, PE, RU, TR |
| **Total** | | **35/87 (40.23%)** | |

**Table 7 Characteristics of authorized drug product database**

| **Specification of special contents for new drugs** | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| -Specify special contents for new drugs | HIC | 7/52 (13.46%) | BE, ES, IS, JP, LT, NL, US |
| | UMIC | 1/52 (1.92%) | TH |
| **Total** | | **8/52 (15.38%)** | |
| -Not specify special contents for new drugs | HIC | 29/52 (55.77%) | AT, AU, CA, CH, CZ, DK, EE, FI, FR, HK, HU, HR, IS, IE, IL, IT, LV, MT, NZ, NO, PT, RO, SA, SE, SI, SK, SG, TT, UK |
| | UMIC | 16/52 (30.77%) | AL, AR, AM, AZ, BG, BR, BY, CN, ID, IR, MK, MY, NA, RS, VE, ZA |
| **Total** | | **45/52 (86.54%)** | |
| **Providing drug information** | | | |
| -Provide drug information | HIC | 19/52 (36.54%) | AT, AU, BE, CZ, ES, FI, HR, HU, IS, IE, IT, JP, MT, NL, NZ, PT, SK, UK, US |
| | UMIC | 5/52 (9.62%) | AR, AM, MY, RS, VE |
| **Total** | | **24/52 (46.16%)** | |
| -Not provide drug information | HIC | 16/52 (30.77%) | CA, CH, DK, EE, FR, HK, IL, LV, LT, NO RO, SA, SE, SI, SG, TT |
| | UMIC | 12/52 (23.07%) | AL, AZ, BG, BR, BY, CN, ID, IR, MK, NA, TH, ZA |
| **Total** | | **28/52 (53.84%)** | |



**Public accessibility of ADR reports**

Public accessibility of ADR reports was available in 7 high income countries (8.05%) including Australia, Canada, the Netherlands, New Zealand, Singapore, the United Kingdom and the United States as well as European database of ADR reports. Healthcare professionals and consumers were allowed to publicly access database of ADR reports with limited data including patients' information (age, gender),

drugs' name and adverse events. The United States provided the most contents for data of ADR reports. Information on searchable database of ADR reports was not assessed the causal relationship between suspected drugs and the reported adverse events. Public accessibility of ADR reports was shown in table 8. (Appendix F)

**Table 8 Public accessibility of ADR reports**

| | Income level | Number (%) | Countries name |
|---|---|---|---|
| **Public accessibility of ADR reports** | HIC | 7/87 (8.05%) | AU, CA, NL, NZ, SG, UK, US |
| | UMIC | - | - |
| **Total** | | **7/87 (8.05%)** | |
| **No public accessibility of ADR reports** | HIC | 46/87 (52.87%) | AD, AE, AT, BB, BE, BN, CH, CL, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HK, HR, HU, IE, IL, IS, IT, JP, KR, LI, LT, LU, LV, MT, MU, NC, NO, OM, PA, PL, PT, RO, SA, SE, SI, SK, TT, TW, UY |
| | UMIC | 34/87 (39.08%) | AL, AM, AR, AZ, BA, BG, BR, BW, BY, BZ, CN, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, ME, MK MY, MX, NA, PE, RS, RU, TH, TR, VE, ZA |
| **Total** | | **80/87(91.95%)** | |



**PRE-MARKETING: Risk management plan**

RMP product coverage scope, global RMP and local RMP submission, and publication of approved RMP were presented in table 9 and table 10. (Appendix G and Appendix H)

**RMP product coverage scope**

RMP was desired in 49 countries (56.32%). Of these, 47 countries (54.02%) required RMP for all types of new drugs whereas 2 countries (2.30%) requested RMP for some types of new drugs. Singapore required RMP for new chemical entities and biologic products while Thailand desired RMP for only biologic products and biosimilars. In contrast, 38 countries (43.67%) did not specify RMP requirement.

**Table 9 RMP product coverage scope requirement**

| **RMP requirement** | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| Require RMP<br>-Cover all types of new drugs | HIC | 40/87 (45.98%) | AE, AT, AU, BE, CA, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IS, IE, IT, JP, KR, LV, LT, LU, MT, NL, NZ, NO, OM, PL, PT, RO, SA, SE, SI, SK, TW, UK, US |
| | UMIC | 7/87 (8.04%) | BR, BG, CN, MY, NA, RU, TR |
| Require RMP<br>-Cover some types of new drugs | HIC | 1/87 (1.15%) | SG (new chemical entities and new biologic products) |
| | UMIC | 1/87 (1.15%) | TH (new biologic products and biosimilar) |
| **Total** | | **49/87 (56.32%)** | |
| Not specify RMP | HIC | 12/87 (13.79%) | AD, BB, BN, CL, HK, IL, LI, MU, NC, PA, TT, UY |
| | UMIC | 26/87 (29.88%) | AL, AM, AR, AZ, BA, BW, BY, BZ, CO, CR, CU, DO, GT, ID, IR, IQ, JO, JM, KZ, ME, MK, MX, PE, RS, VE, ZA |
| **Total** | | **38/87 (43.67%)** | |

**Global, local RMP submission and publication of approved RMP**

Forty-five countries (91.84%) required global RMP without local RMP. Both global and local RMP were desired in 4 countries (8.16%) including Australia, Canada, Singapore and Thailand. Publication of approved RMP to reveal transparency of post-marketing surveillance activities ware available on drug regulatory authority websites in 34 countries (69.39%). Of these, 29 countries (59.18%) as EMA member states provided link to EU-RMP publication while 5 countries (10.20%) including Australia, Japan, Switzerland, the United Kingdom and the United States published approved RMP on their websites.

**Table 10 RMP submission and publication of approved RMP in countries with RMP requirement**

| | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| **RMP submission** | | | |
| -Global RMP without local RMP | HIC | 38/49 (77.55%) | AE, AT, BE, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IS, IE, IT, JP, KR, LV, LT, LU, MT, NL, NZ, NO, OM, PL, PT, RO, SA, SE, SI, SK, TW, UK, US |
| | UMIC | 7/49 (14.29%) | BR, BG, CN, MY, NA, RU, TR |
| **Total** | | **45/49 (91.84%)** | |
| -Global RMP and local RMP | HIC | 3/49 (6.12%) | AU, CA, SG |
| | UMIC | 1/49 (2.04%) | TH |
| **Total** | | **4/49 (8.16%)** | |

| | Income level | Number (%) | Countries name |
|---|---|---|---|
| **Publication of approved RMP** | | | |
| -Available on DRA website | HIC | 33/49 (67.35%) | AT, AU, BE, CH, CY, CZ, DK, EE, ES, FI, DE, FR, GR, HU, HR, IE, IS, IT, JP, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK, UK, US |
| | UMIC | 1/49 (2.04%) | BG |
| **Total** | | **34/49 (69.39%)** | |
| -Not available on DRA website | HIC | 8/49 (16.33%) | AE, CA, KR, NZ, OM, SA, SG, TW |
| | UMIC | 7/49 (14.28%) | BR, CN, MY, NA, RU, TH, TR |
| **Total** | | **15/49 (30.61%)** | |

As aforementioned issues, all 49 countries (56.32%) required EU-RMP or US-risk evaluation mitigation and strategies (REMS). The core components of EU-RMP and US-REMS included risk concerned, risk minimization measures and timetable of post-approval RMP assessment. The differences were that EU addressed post-authorization safety studies in RMP whereas US did not include post-authorization safety studies in REMS. US post-authorization safety studies were mentioned in the review of initial application. EU-RMP stated important identified risks, important potential risks and important missing information while US-REMS mentioned only important identified risks. For risk minimization measures, materials including guidance for prescribing, dispensing and patients' brochures were desired in both EU-RMP and US-REMS. Particularly, US-REMS provided information regarding the distribution of REMS directly to healthcare professionals. US pharmaceutical companies must send REMS letters via e-mail within 30 days or 60 days from the date of new drug launched, again 12 months

later and report number of healthcare professionals targeted by REMS whereas EU did not mention timing of informing RMP to healthcare professionals. In addition, US-REMS required certified physicians who passed the prescriber knowledge assessment by answering the questions about new drugs while EU-RMP mentioned the study to assess healthcare professionals' knowledge regarding educational materials. For timetable of post-approval RMP or REMS assessment, the updated EU-RMP could be submitted anytime when new risk occurred or along with PSUR while US-REMS was required at 6 months, 12 months, and annually thereafter from the date of the initially approved REMS.

**POST-MARKETING: Risk collection, Risk assessment, Risk communication and Pharmacovigilance inspection**

**Risk collection**

Risk collection included post-authorization safety studies, pre-specified monitoring period, ADR reporting channels and time to report ADR. The special issues for new drugs were mentioned in post-authorization safety studies and pre-specified monitoring period.



**Post-authorization safety studies**

Forty-three countries (49.43%) required pharmaceutical companies to carry out post-authorization safety studies. Of these, 42 countries (48.28%) desired drug companies to conduct post-authorization safety studies including observational studies and post-marketing clinical trials to gather safety for all

type of new drugs. Only one country (1.15%), Thailand monitored new drugs with condition pursuant to risk level. New drugs with risk level 1 approved with clinical trial phase 2 required drug companies to conduct active vigilance such as registry for all cases every visit while new drugs with risk level 2 (new chemical entities, new indication, new combination, new biological products) and new drugs with risk level 3 (new delivery system, new route of administration, new dosage form, new strength) were monitored by using intensified reporting system. In addition, 2 countries (2.30%) including Japan and Thailand performed intensified reporting system. Japan was the pioneer to initiate early post-marketing phase vigilance (EPPV). It was the intensified reporting system during the first 6 months after new drugs were approved. The strategies were that medical representatives provided information 2 weeks before new drug delivery to hospitals. At post-launching, medical representatives also reminded healthcare professional to report ADR every 2 weeks in the first 2 months and once a month for the following 4 months. Thailand adopted and adapted this concept from Japan. The differences were that Thailand required pharmaceutical companies to provide information 1 month before launching and reminding healthcare professionals to report ADR every 2 months in the first 6 months. On the other hand, 44 countries (50.57%) did not require post-authorization safety studies for new drugs. Requirement of post-authorization safety studies was presented in table 11. (Appendix I)

**Table 11 Risk collection: post-authorization safety study (PASS) requirement**

| PASS requirement | Income level | Number (%) | Countries name |
|---|---|---|---|
| Require PASS for all types of new drugs | HIC | 38/87 (43.68%) | AT, AU, BE, CA, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IS, IE, IT, JP, KR, LV, LT, LU, MT, NL, NZ, NO, PL, PT, RO, SE, SG, SI, SK, TW, UK, US |
| | UMIC | 4/87 (4.60%) | BR, BG, CN, TR |
| Required PASS for new drugs approved with clinical trial phase 2 | UMIC | 1/87 (1.15%) | TH |
| **Total** | | **43/87 (49.43%)** | |
| Not require PASS | HIC | 15/87 (17.24%) | AD, AE, BB, BN, CL, HK, IL, LI, MU, NC, OM, PA, SA, TT, UY |
| | UMIC | 29/87 (33.33%) | AL, AM, AR, AZ, BA, BW, BY, BZ, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, ME, MK, MY, NA, MX, PE, RU, RS, VE, ZA |
| **Total** | | **44/87 (50.57%)** | |

**Pre-specified monitoring period**



Pre-specified monitoring period for new drugs was presented in table 12 and table 13. Forty-three countries (49.43%) required pre-specified monitoring for new drugs. Fixed pre-specified monitoring period was found in 39 countries (44.83%). Of these, 38 countries requested to monitor all types of new drugs during the first 5 years after approval except the United Kingdom that pre-specified monitoring period was 2 years. Pre-specified monitoring period depending on types of new drugs was revealed in 4 countries (4.60%) including China (3-5 years), Japan (4-8 years), Korea (4-6 years) and Thailand (1-2 years). New active ingredient or new chemical entity seemed

to be monitored longer than other types of new drugs. On the other hand, 44 countries (50.57%) did not mention pre-specified monitoring period for new drugs.

**Table 12 Risk collection: pre-specified monitoring period**

| **Pre-specified monitoring period** | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| -Fixed monitoring period 5 years | HIC | 35/87 (40.23%) | AT, AU, BE, CA, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IS, IE, IT, LV, LT, LU, MT, NL, NZ, NO, PL, PT, RO, SE, SG, SI, SK, TW, US |
| | UMIC | 3/87 (3.45%) | BR, BG, TR |
| -Fixed monitoring period 2 years | HIC | 1/87 (1.15%) | UK |
| | UMIC | - | - |
| -Monitoring period depended on types of new drugs | HIC | 2/87 (2.30%) | JP (4-8 years)<br>KR (4-6 years) |
| | UMIC | 2/87 (2.30%) | CN (3-5 years)<br>TH (1-2 years) |
| **Total** | | **43/87 (49.43%)** | |
| Not require pre-specified monitoring period | HIC | 15/87 (17.24%) | AD, AE, BB, BN, CL, HK, IL, LI, MU, NC, OM, PA, SA, TT, UY |
| | UMIC | 29/87 (33.33%) | AL, AM, AR, AZ, BA, BW, BY, BZ, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, ME, MK, MY, NA, MX, PE, RU, RS, VE, ZA |
| **Total** | | **44/87 (50.57%)** | |

**Table 13 Risk collection: pre-specified monitoring period depended on types of new drugs**

| Countries | Types of new drugs | Pre-specified monitoring period |
|---|---|---|
| Japan | New active ingredient<br>New route of administration<br>New combination, new indication, new strength | 8 years<br>6 years<br>4-6 years |
| Korea | New active ingredient, new route of administration, new combination<br>New indication | 6 years<br>4 years |
| China | New active ingredient<br>New dosage form, new delivery system, new route of administration, new combination<br>New indication, new salt of previously approved | 5 years<br>4 years<br>3 years |
| Thailand | New drug with risk level 1 (approval with clinical trial phase 2)<br>New drug with risk level 2 (new chemical entity, new indication, new combination, new biological)<br>New drug with risk level 3 (new delivery system, new route of administration, new dosage form, new strength) | At least 2 years<br>2 years<br>1 year |

**ADR reporting channels**



Seventy-nine countries (90.80%) had website for ADR reporting plus post, phone, fax and e-mail whereas ADR reporting via website was not available in 8 countries (9.20%). These countries reported ADR via post, phone, fax and e-mail. Furthermore, 7 countries (8.05%) included 6 high income countries (6.90%); Croatia, the Netherlands, New Zealand, Oman, Singapore, the United Kingdom and 1 upper-middle income country; Botswana (1.15%) which adopted smartphone application to report ADR complementing the conventional routes. ADR reporting channels were presented in table 14. (Appendix J, Appendix K)

**Table 14 Risk collection: ADR reporting channels**

| ADR reporting channels | Income level | Number (%) | Countries name |
|---|---|---|---|
| Website for ADR reporting plus post, phone, fax and e-mail | HIC | 48/87 (55.17%) | AD, AT, AU, BB, BE, CA, CL, HR, CY, CZ, DK, EE, FI, FR, DE, GR, HK, HU, IS, IE, IL, IT, JP, KR, LV, LT, LU, MT, MU, NL, NZ, NO, OM, PL, PT, RO, SA, SG, SK, SI, ES, SE, CH, TW, TT, AE, UK, US |
| | UMIC | 31/87 (35.63%) | AL, AR, AM, AZ, BY, BZ, BA, BW, BR, BG, CN, CO, CU, DO, ID, IR, IQ, JM, JO, KZ, MY, MX, ME, NA, MK, RU, RS, ZA, TH, TR, VE |
| **Total** | | **79/87 (90.80%)** | |
| No website for ADR reporting | HIC | 5/87 (5.75%) | BN, LI, NC, PA, UY |
| | UMIC | 3/87 (3.45%) | CR, GT, PE |
| **Total** | | **8/87 (9.20%)** | |

**Time to report ADR**

Sixty-eight countries (78.17%) defined time to report serious ADR whereas 19 countries (21.83%) did not specify time to report serious ADR. Mostly, time to report serious ADR was required within 15 days in 61 countries (70.12%). Moreover, 9 countries required time to rapidly report fatal cases. Thailand and Brunei Darussalam requested fatal cases within 24 hours while Armenia, Brazil, Japan, Malaysia, Mexico, Russia and Taiwan desired 7 days to report fatal cases. Time to report serious ADR was shown in table 15.

Forty-five countries (51.72%) defined time to report non-serious ADR whereas 42 countries (48.28%) did not specify time to report non-serious ADR. Generally, time to report non-serious ADR was desired within 90 days in 35 countries (40.22%). Time to report serious ADR and non-serious ADR was presented in table 16. (Appendix J)

**Table 15 Risk collection: time to report serious ADR**

| **Time to report serious ADR** | **HIC number (%)** | **Countries name** | **UMIC number (%)** | **Countries name** | **Total** |
|---|---|---|---|---|---|
| Specify time to report serious ADR | 45/87 (51.73%) | | 23/87 (26.44%) | | **68/87 (78.17%)** |
| 24 hours | - | - | 2/87 (2.30%) | CR, PE | |
| 72 hours | - | - | 2/87 (2.30%) | CO, CU | |
| 5 days | 1/87 (1.15%) | PA | - | - | |
| 7 days | 1/87 (1.15%) | BN | - | - | |
| 15 days | 43/87 (49.43%) | AT, AU, BE, CA, HR, CY, CZ, DK, EE, FI, FR, DE, GR HK, HU, IS, IE, IT, JP, KR LV, LT, LU, MT, MU, NL, NZ, NO, OM, PL, PT, RO, SA, SG, SK, SI, ES, SE, CH TW, AE, UK, US | 18/87 (20.69%) | AR, AM, BG, BR, BW, CN, GT, ID, JM, JO, MX, MY, NA, RS, RU, TH, TR, ZA | |
| 30 days | - | - | 1/87 (1.15%) | IQ | |
| Not specify time to report serious ADR | 8/87 (9.19%) | AD, BB, CL, IL, LI, NC, TT, UY | 11/87 (12.64%) | AL, AZ, BA, BY, BZ, DO, IR, KZ, ME, MK, VE | **19/87 (21.83%)** |

**Table 16 Risk collection: time to report non-serious ADR**

| **Time to report non-serious ADR** | **HIC number (%)** | **Countries name** | **UMIC number (%)** | **Countries name** | **Total** |
|---|---|---|---|---|---|
| Specify time to report non-serious ADR | 36/87 (41.42%) | | 9/87 (10.30%) | | **45/87 (51.72%)** |
| 7 days | 1/87 (1.15%) | BN | - | - | |
| 15 days | 3/87 (3.45%) | KR, NZ, OM | 2/87 (2.30%) | BR, BW | |
| 30 days | - | - | 2/87 (2.30%) | MX, ID | |
| 60 days | - | - | 1/87 (1.15%) | TH | |
| 90 days | 32/87 (36.77%) | AE, AT, BE, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HU, HR, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SA, SE, SI, SK, UK | 3/87 (3.45%) | BG, JM, JO | |
| 180 days | - | - | 1/87 (1.15%) | IQ | |
| Not specify time to report non-serious ADR | 17/87 (19.54%) | AD, AU, BB, CA, CL, HK, IL, JP, LI, MU, NC, PA, SG, TT, TW, US, UY | 26/87 (29.89%) | AL, AR, AM, AZ, BA, BY, BZ, CN, CO, CR, CU, DO, GT, IR, KZ, ME, MY, MK, NA, PE, RS, RU, TR, VE, ZA | **42/87 (48.28%)** |

**Risk assessment**

Risk assessment consisted of periodic safety update report (PSUR) submission interval, application of risk assessment output, publication of risk assessment reports and risk assessment committee.

**PSUR submission interval**

Sixty-six countries (75.86%) defined PSUR submission interval whereas 21 countries (24.14%) did not specify time to submit PSUR. Sixty-three countries (72.41%) required to submit PSUR 6 monthly for the first two years after approval. Two countries (2.30%), Argentina required to submit PSUR annually while Cuba requested to submit PSUR annually for the first 3 years, then every 5 years and 10 years. One country (1.15%), Thailand requested to submit PSUR 4 monthly. PSUR submission interval was presented in table 17. At regional level, EMA particularly specified reference date lists for PSUR submission. (Appendix L)

**Table 17 Risk assessment: PSUR submission interval**

| **PSUR submission interval** | **HIC Number (%)** | **Countries name** | **UMIC number (%)** | **Countries name** | **Total** |
|---|---|---|---|---|---|
| Specify PSUR submission interval | 46/87 (52.87%) | | 20/87 (22.99%) | | **66/87 (75.86%)** |
| Every 4 months in the first 2 years | - | - | 1/87 (1.15%) | TH | |
| Every 6 months in the first 2 years | 46/87 (52.87%) | AE, AT, AU, BE, BN, CA, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HU, HR, IE, IS, IL, IT, JP, KR, LI, LT, LU, LV, MT, MU, NL, NO, NZ, OM, PL, PT, RO, SA, SE, SG, SI, SK, TW, UK, US, UY | 17/87 (19.54%) | AM, BG, BR, BW, BY, CN, CO, IQ, JM, JO, KZ, MX, NA, RU, RS, TR, ZA | |
| Annually | - | - | 2/87 (2.30%) | AR, CU | |
| Not specify PSUR submission interval | 7/87 (8.05%) | AD, BB, CL, HK, NC, PA, TT | 14/87 (16.09%) | AL, AZ, BA, BZ, CR, DO, GT, ID, IR, ME, MK, MY, PE, VE | **21/87 (24.14%)** |



**Application of risk assessment output**

Thirty countries (34.48%) processed risk assessment for taking regulatory action and removing new drugs from condition whereas 57 countries (65.52%) operated risk assessment only for taking regulatory action. Application of risk assessment output was illustrated in table 18.

**Table 18 Risk assessment: application of risk assessment output**

| **Application of risk assessment output** | **Income level** | **number (%)** | **Countries name** |
|---|---|---|---|
| Take regulatory action and remove new drugs from condition | HIC | 28/87 (32.18%) | AT, BE, CY, CZ, DE, DK, EE, ES FI, FR, GR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SE, SI, SK |
| | UMIC | 2/87 (2.30%) | BG, TH |
| **Total** | | **30/87 (34.48%)** | |
| Take regulatory action | HIC | 25/87 (28.74%) | AD, AE, AU, BB, BN, CA, CH, CL, HK, IL, JP, KR, LI, MU, NC, NZ, OM, PA, SA, SG, TT, TW, UK, US, UY |
| | UMIC | 32/87 (36.78%) | AL, AM, AR, AZ, BA, BR, BW, BY, BZ, CN, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, MY, ME, MK, MX, NA, PE, RS, RU, TR, VE, ZA |
| **Total** | | **57/87 (65.52%)** | |

**Publication of risk assessment reports**

Risk assessment reports for taking regulatory action were published on drug regulatory authority websites in 8 high income countries (9.20%) including Australia, Canada, Croatia, Denmark, Germany, New Zealand, the United Kingdom and the United States. Solely EMA and Thailand assessed benefit-risk balance to remove new drugs from condition. However, the publication of risk assessment reports for removing new drugs from condition was only found at EU regional level. Thailand did not issue the publication of assessment reports for removing new drugs from condition. The contents in risk assessment reports included the committee's discussion on data in PSUR to weigh the benefit-risk balance of medicinal products. Publication of risk assessment reports was presented in table 19. (Appendix L)

**Table 19 Risk assessment: publication of risk assessment report**

| **Publication of risk assessment reports** | **Income level** | **Number (%)** | **Countries name** |
|---|---|---|---|
| Publication of risk assessment report | HIC | 8/87 (9.20%) | AU, CA, DE, DK, HR, NZ, UK, US |
| | UMIC | - | - |
| **Total** | | **8/87 (9.20%)** | |
| No publication of risk assessment report | HIC | 45/87 (51.72%) | AD, AE, AT, BB, BE, BN, CH, CL, CY, CZ, EE, ES, FI, FR, GR, HK, HU, IE, IL, IS, IT, JP, KR, LI, LT, LU, LV, MT, MU, NC, NL, NO, OM, PA, PL, PT, RO, SA, SE, SG, SK, SI, TT, TW, UY |
| | UMIC | 34/87 (39.08%) | AL, AR, AM, AZ, BA, BG, BR, BW, BY, BZ, CN, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, ME, MK, MX, MY, NA, PE, RS RU, TH, TR, VE, ZA |
| **Total** | | **79/87 (90.80%)** | |

**Risk assessment committee**

Lists of risk assessment committee were issued on medicines regulatory authority websites in 20 countries (22.99%). Of these, committee in 16 countries (80.00%) consisted of regulatory authorities and experts. Committee in 2 countries (10.00%) including New Zealand and the United Kingdom included regulatory authorities, experts and lay representatives. Committee in 2 countries (10.00%) including Denmark and the United States composed regulatory authorities, experts, lay representatives and drug company representatives. The experts' area were pharmacology, pharmacovigilance and medicines. On the other hand, 67 countries (77.01%) did not publish lists of risk assessment committee on DRA website. Risk

assessment committee was shown in table 20. Risk assessment for new drugs and non-new drugs was operated by the same committee. (Appendix M)

**Table 20 Risk assessment committee**

| **Risk assessment committee** | **HIC number (%)** | **Countries name** | **UMIC number (%)** | **Countries name** | **Total** |
|---|---|---|---|---|---|
| Publication of risk assessment committee lists | 18/87 (20.69%) | AT, AU, BE, CH, DK, ES, FR, HR IE, IS, JP, MU, NL, NZ, SG, SK, UK, US | 2/87 (2.30%) | BA, BG | **20/87 (22.99%)** |
| Components of risk assessment committee | | | | | |
| -Regulatory authorities<br>-Expert | 14/20 (70.00%) | AT, AU, BE, CH, ES, FR, HR IE, IS, JP, MU, NL, SG, SK, | 2/20 (10.00%) | BA, BG | |
| -Regulatory authorities<br>-Expert<br>-Lay representatives | 2/20 (10.00%) | NZ, UK | - | - | |
| -Regulatory authorities<br>-Expert<br>-Lay representatives<br>-Drug company representatives | 2/20 (10.00%) | DK, US | - | - | |
| No publication of risk assessment committee lists | 35/87 (40.23%) | AD, AE, BB, BN, CA, CL, CY, CZ, DE, EE, FI, GR, HK, HU, IL, IT, KR, LI, LT, LU, LV, MT, NC, NO, OM, PA, PL, PT, RO, SA, SE, SI, TT, TW, UY | 32/87 (36.78%) | AL, AM, AR, AZ, BR, BW, BY, BZ, CN, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, ME, MK, MY, MX, NA, PE, RU, RS, TH, TR, VE, ZA | **67/87 (77.01%)** |

**Risk communication**

Direct healthcare professional communication (DHPC) prepared by drug companies and bulletin/newsletter launched by national regulatory authorities were types of risk communication. Risk communication channels were presented in table 21 and table 22. (Appendix N)

**DHPC**

Thirty-one countries (35.64%) provided risk communication channels for DHPC. Of these, 24 countries (27.59%) published DHPC on drug regulatory authority websites. Four high income countries (4.60%) including Iceland, Ireland, Latvia and the Netherlands conveyed DHPC via e-mail. Three high income countries (3.45%) including Croatia, Norway and Romania circulated DHPC by both website and e-mail. There was no DHPC available on websites in 56 countries (64.36%).

**Table 21 Risk communication channels: direct healthcare professional communication (DHPC)**



| Risk communication channels | HIC number (%) | Countries name | UMIC number (%) | Countries name | Total |
|---|---|---|---|---|---|
| Providing risk communication channels | 26/87 (29.89%) | | 5/87 (5.75%) | | **31/87 (35.64%)** |
| E-mail | 4/87 (4.60%) | IS, IE, LV, NL | - | - | |
| Website | 19/87 (21.84%) | AT, BE, CH, CA, DE, ES, DK, HU, JP, KR, LT, MT NZ, SE, SG, SI, SK, UK, US | 5/87 (5.75%) | AM, AZ, ME, TH, ZA | |
| Website plus e-mail | 3/87 (3.45%) | HR, NO, RO | - | - | |

| Risk communication channels | HIC number (%) | Countries name | UMIC number (%) | Countries name | Total |
|---|---|---|---|---|---|
| Not available on website | 27/87 (31.03%) | AD, AE, AU, BB, BN, CL, CY, CZ, EE, FI, FR, GR, HK, IL, IT, LI, LU, MU, NC, OM, PA, PL, PT, SA, TT, TW, UY | 29/87 (33.33%) | AL, AR, BA, BG, BR BW, BY, BZ, CN, CO, CR, CU, DO, GT, ID, IR, IQ, JM, JO, KZ, MK, MX, MY, NA, PE, RU, RS, TR, VE | **56/87 (64.36%)** |

**Bulletin/ Newsletter/ News**

Sixty-four countries (73.57%) provided risk communication channels for bulletin/newsletters/news. Forty-three countries (49.43%) issued bulletin, newsletter and news on regulatory authority websites. Sixteen high income countries (18.39%) disseminated by both website and e-mail. Three high income countries (3.45%) including Czech Republic, Latvia and Sweden distributed via website, e-mail and post. Bulgaria as upper-middle income country (1.15%) conveyed through website and post whereas Estonia (1.15%) communicated via e-mail. There was no available bulletin/ newsletter and news on website in 23 countries (26.43%). Particularly, Japan addressed the update lists of new drugs subject to early post-marketing phase vigilance (EPPV) in newsletter every month.

**Table 22 Risk communication channels: newsletter**

| **Risk communication channels** | **HIC number (%)** | **Countries name** | **UMIC number (%)** | **Countries name** | **Total** |
|---|---|---|---|---|---|
| Providing risk communication channels | 44/87 (50.58%) | | 20/87 (22.99%) | | **64/87 (73.57%)** |
| E-mail | 1/87 (1.15%) | EE | - | - | |
| Website | 24/87 (27.59%) | AD, BE, BN, CL, CY, FI, DE, GR, HK, HU, IL, IS, JP[a], KR, LT, OM, PA, RO, SA, SG, SI, SK, TT, TW | 19/87 (21.84%) | AL, AR, AM, AZ, BA BR, BW, BY, CN, CO, CU, ID, KZ, ME, MY, PE, RU, TH, ZA | |
| Website plus post | - | | 1/87 (1.15%) | BG | |
| Website plus e-mail | 16/87 (18.39%) | AU, CH, CA, HR, DK, ES, FR, IE, IT, MT, NL, NO, NZ, PT, UK, US | - | - | |
| Website plus e-mail plus post | 3/87 (3.45%) | CZ, LV, SE | - | - | |
| Not available on website | 9/87 (10.34%) | AE, AT, BB, LI, LU, MU, NC, PL, UY | 14/87 (16.09%) | BZ, CR, DO, GT, IR, IQ, JM, JO, MK, MX, NA, RS, TR, VE | **23/87 (26.43%)** |

a-Japan addressed the update lists of new drugs subject to early post-marketing phase vigilance (EPPV) in newsletter every month.

**Pharmacovigilance inspection**

The purpose of pharmacovigilance inspection was to assess whether drug companies complied with pharmacovigilance obligation. Types of inspection included routine inspection, product-related inspection (e.g. new chemical entities, new biologic products), and event-related inspection (e.g. failure to comply with reporting obligation). Grading of inspection outcome comprised critical deficiencies, major deficiencies and minor deficiencies. Critical was defined as a deficiency which had potential risk to patients. Major was defined as a deficiency which could be potential risks to patients. Minor was defined as a deficiency which did not affect patients. The actions for non-compliance included education and suggestion, reminding the obligation and regulatory actions such as the cancellation or suspension of qualified person for pharmacovigilance (QPPV), and suspension or withdrawal of medicinal products. Pharmacovigilance inspection could be announcement or un-announcement. PV inspection was mentioned in 40 countries (45.98%) whereas 47 countries (54.02%) did not specify PV inspection. Pharmacovigilance inspection was presented in table 23. (Appendix O).



The assessment of pharmacovigilance system of new drugs in Thailand following IPAT and WHO indicators was mentioned in Appendix P. The example of summary report of PV inspection-UK was mentioned in appendix Q. The examples of new drugs with RMP and protocols were addressed in appendix R.

**Table 23 Pharmacovigilance inspection**

| PV inspection | Income level | Number (%) | Countries name |
|---|---|---|---|
| Specify PV inspection | HIC | 35/87 (40.23%) | AT, AU, BE, CA, CY, CZ, DE, DK, EE, ES, FI, FR, GR, HR, HU, IE, IS, IT, JP, LT, LU, LV, MT, NL, NO, OM, PL, PT, RO, SA, SE, SI, SK, UK, US |
| | UMIC | 5/87 (5.75%) | BG, BR, CO, CU, JO |
| **Total** | | **40/87 (45.98%)** | |
| Not specify PV inspection | HIC | 18/87 (20.69%) | AD, AE, BB, BN, CH, CL, HK, IL, KR, LI, MU, NC, NZ, PA, SG, TT, TW, UY |
| | UMIC | 29/87 (33.33%) | AL, AM, AR, AZ, BA, BW, BY, BZ, CN, CR, DO, GT, ID, IR, IQ, JM, KZ, MY, ME, MK, MX, NA, PE, RS, RU, TH, TR, VE, ZA |
| **Total** | | **47/87 (54.02%)** | |

**Results of the second objective: Assessment of pharmacovigilance system of new drugs in Thailand**

A total number of 36 key informants were interviewed. Six pharmacists from Thai FDA (3 pre-marketing regulatory authorities (Pre-Thai FDA), 3 post-marketing regulatory authorities (Post-Thai FDA). Six pharmacists from 6 drug companies (4 multinational drug companies (MNC), 2 distributor drug companies (DTC)). Sixteen pharmacists from 8 hospitals (5 university hospitals (UH), 3 tertiary hospitals (TH)). Eight physicians from 5 hospitals (3 university hospitals (UH) and 2 tertiary hospitals (TH)).

The results were presented following the framework including structures, processes and outputs. Structure of RMP included RMP guideline. Processes of RMP encompassed RMP submission, RMP update and inspection. Structures of SMP consisted of SMP guideline, SMP protocol and national database of approved drugs. Processes of SMP comprised the distribution of safety information, methods of monitoring new drugs with SMP in drug companies and hospitals, ADR reporting to Thai FDA, risk assessment and risk communication. Outputs were the number of ADRs reporting new drugs with SMP, number of signal detections of new drugs with SMP, regulatory action taken and actual monitoring period.

**Structure of RMP**

**RMP Guideline**

The purpose of RMP guideline was to facilitate relevant stakeholders to implement RMP activities in real practice. All relevant stakeholders should have awareness and understanding of RMP guideline. Awareness of RMP guideline and understanding of RMP guideline (clarity of RMP guideline and RMP product coverage scope) were described. Summaries of RMP were presented in table 24.

**Awareness of RMP guideline**

All 6 regulatory authorities (100.00%) and all 6 drug companies (100.00%) reached RMP guideline. Of these 6 regulatory authorities, 3 regulatory authorities received training on RMP guideline organized within pre-marketing division once time (Pre-Thai FDA2, Pre-Thai FDA3, Post-Thai FDA1 director). Two regulatory authorities received notification document of RMP guideline (Post-Thai FDA2, Post-Thai FDA3). One regulatory authority who was the expert informed the official RMP guideline after announcement. The targeted audiences were drug companies (Pre-Thai FDA1 expert). All 6 drug companies (100.00%) received RMP guideline from PREMA. It indicated that all regulatory authorities and all drug companies were aware RMP guideline.

*"RMP conference was arranged within pre-marketing division once time. The audiences were regulatory authorities from pre-marketing division and post-marketing division. The contents refer to EU-RMP." (Pre-Thai FDA2).*

**Understanding of RMP guideline**

Understanding of RMP guideline included clarity of RMP guideline and RMP product coverage scope

**Clarity of RMP guideline**

All regulatory authorities (100.00%) and all 6 drug companies (100.00%) agreed that RMP guideline was clear. In addition, there were suggestions from 2 regulatory authorities. The first suggestion was that Thai RMP guideline needed to be in greater detail like EU-RMP (Pre-Thai FDA2). Another recommendation was that RMP needed to mention about model or scenario for different risk situation regarding risk minimization measures (Post-Thai FDA2).



**RMP product coverage scope**

Six key informants (50.00%) agreed with RMP product coverage scope whereas 4 key informants (33.33%) disagreed with RMP product coverage scope and 2 key informants (16.67%) did not concern with RMP product coverage scope. The reasons for this were explained as follows:

Agreement with RMP product coverage scope

Six key informants (50.00%) agreed with RMP product coverage scope. Of these, 3 regulatory authorities agreed that RMP covered only biologic products because biologic products had more complicated molecule contributing to higher risk than chemical products (Pre-Thai FDA3, Post-Thai FD2, Post-Thai FDA3). One regulatory authority agreed that RMP covered biologic products first due to higher risk. Then, RMP could also extend to cover specified chemical products (Pre-Thai FDA1 expert). Two drug companies agreed that RMP was appropriate to cover only biologic products. It was in line with the most products in drug companies were biologic products (MNC3, DTC2).

*"It was suitable that RMP covered biologic products because these biologic products possessed complex molecules leading to more severe risks than chemical molecules. In addition, unpredictable stabilities could alter immunogenicity." (Pre-Thai FDA3)*



*"I thought that RMP was properly required for only biologic products. Most products in drug company were biologic. If RMP covered chemical products, it would be a burden." (DTC2).*

Disagreement with RMP product coverage scope

Four key informants (33.33%) disagreed with RMP product covering only biologic products. Of these, 2 regulatory authorities expressed that RMP should also be requested for chemical products because both biologic products and chemical products possessed risks (Pre-Thai FDA2, Post-Thai FDA1 director). Two drug companies commented that products required to submit RMP should be considered according to their risks. It should not depend on biologic products or chemical products (MNC4, DTC1).

*"In my opinion, both biologic products and chemical products had risks. Thai FDA should announce which biologic products and chemical products are subject to submit RMP. Thai FDA might specify group of products such as anti-cancer." (DCT1)*

Un-concerned on RMP product coverage scope

Two drug companies (16.67%) did not concern that RMP required to cover only biologic products. The reason for this was that these drug companies were globally mandated to implement RMP for both biologic products and chemical products (MNC1, MNC 2).



According to RMP guideline, all regulatory authorities and all drug companies were aware and understood RMP guideline. In addition, most key informants accepted that RMP product coverage scope required for biologic products was appropriate.

**Processes of RMP**

Processes of RMP included RMP submission, RMP update and inspection.

**RMP submission**

RMP submission was detailed in terms of responsible person, principle of RMP review and global RMP/local RMP submission. The purpose of RMP submission was to ensure that drug companies addressed complete safety specification, appropriate risk minimization activities and appropriate pharmacovigilance activities in RMP.

**Responsible person**

Pre-marketing regulatory authorities were mainly responsible for RMP review whereas post-marketing regulatory authorities did not involve in the process of RMP review. It was individual pre-marketing regulatory authorities' decision. There was no RMP committee.



*"Pre-marketing division made an attempt to collaborate with post-marketing division to set up a formal RMP committee. It was in process of establishing platform." (Pre-Thai FDA2)*

**Principle of RMP review**

There were no standard criteria for RMP review. The major principle of RMP review was consistent among pre-marketing regulatory authorities. They considered the completeness of safety specification, the appropriateness of risk minimization activities and the appropriateness of pharmacovigilance activities.

Particularly, the local additional risk minimization activities and local additional pharmacovigilance activities were emphasized.

Safety specification mainly followed global RMP with focusing on safety concern for Thai population. For local additional risk minimization activities, not all biologic products needed educational materials. Regulatory authorities considered case by case if routine risk minimization activities were not enough. For local additional pharmacovigilance activities, regulatory authorities pondered risk level in order to check whether it needed to mention active vigilance for new drugs with SMP risk level 1 in RMP. From drug companies' perspective, there was no problem regarding RMP review. RMP was approved with other dossiers at the time of authorization. Regulatory authorities confirmed that the compliance of drug companies was good in addressing complete safety specification, appropriate risk minimization activities and appropriate pharmacovigilance activities.



**Global RMP and local RMP submission**

The purpose of global RMP submission was used as reference whereas the aim of local RMP submission was to address local activities implemented in Thailand.

Pre-marketing regulatory authorities required both global RMP and local RMP. In real practice, some drug companies submitted both global RMP and local RMP while some drug companies submitted only global RMP. There was the absence of local RMP submission due to no enforcement. Therefore, there was the

feedback to these drug companies to prepare and submit local RMP. It indicated that the compliance of drug companies was good in global RMP submission. However, the compliance of drug companies was partially good in local RMP submission.

All 6 drug companies (100.00%) confirmed that they submitted both global RMP and local RMP to Thai FDA. There was no problem in preparing and submitting RMP in 5 drug companies (83.33%). However, only one drug company (16.67%) mentioned that drug company must translate local RMP into English in order to globally approve. As consequence of this, it would take time and be burden (DTC2).

*"Both global RMP and addendum local RMP were required. Global RMP provided the whole pictures of medicinal products whereas local RMP addressed specific activities that were planned to implement in Thailand. Some drug companies submitted both global RMP and local RMP while some drug companies submitted only global RMP." (Pre-Thai FDA2)*



*"Both global RMP and local RMP were requested. I experienced from covid vaccine, only one drug company submitted both global RMP and local RMP while other drug companies submit only global RMP. I fed back the comments to these drug companies to submit local RMP as well." (Pre-Thai FDA3)*

**RMP update**

The purpose of RMP update was to add new safety in RMP. All relevant stakeholders should have awareness of the importance of RMP update and compliance on RMP update.

Pre-marketing regulatory authorities had function to review updated RMP during post-marketing phase whereas post-marketing regulatory authorities did not pertain in the reviewing of updated RMP. There was no timetable to submit updated RMP. Drug companies could submit anytime throughout drug product life cycle.

All six regulatory authorities (100.00%) and all six drug companies (100.00%) were aware of the importance of RMP update. Regulatory authority experienced in receiving updated RMP from drug companies and confirmed that drug companies updated RMP in part of new safety specification as well as amended patient information leaflet. For instance, new safety such as covid vaccine induced thromboembolism. It indicated that the compliance of drug companies was good in RMP update.

**Inspection**



The purpose of inspection was to evaluate whether drug companies complied with pharmacovigilance obligation. There was no inspection due to lack of policy from pre-marketing regulatory authority's perspective (Pre-Thai FDA1 expert), lack of staff and lack of knowledge in inspection from post-marketing regulatory authority's perspective (Post-Thai FDA1 director).

According to RMP processes, the achievable components were that the compliance of drug companies was good in addressing complete safety specification, appropriate risk minimization activities and appropriate pharmacovigilance activities as

well as RMP update. However, the unachievable element was the absence of PV inspection.

**Structures of SMP**

Structures of SMP included SMP guideline, SMP protocol and national database of approved drugs. Summaries of SMP structures were shown in table 25.

**SMP guideline**

The purpose of SMP guideline was to facilitate relevant stakeholders to implement SMP activities into real practice. Relevant stakeholders should have awareness and understanding of SMP guideline. Awareness of SMP guideline and understanding of SMP guideline (clarity of SMP guideline and opinion on SMP risk-based approach) were explained.

**Awareness of SMP guideline**

All 6 regulatory authorities (100.00%) and all 6 drug companies (100.00%) reached SMP guideline. Of these 6 regulatory authorities, 2 regulatory authorities accessed SMP guideline on Thai FDA website (Pre-Thai FDA2, Post-Thai FDA3) whereas 2 regulatory authorities received SMP guideline from notification document within organization (Pre-Thai FDA3, Post-Thai FDA2). Other 2 regulatory authorities involved in informing official SMP guideline after announcement to drug companies (Pre-Thai FDA1 expert, Post-Thai FDA1 director). Targeted audiences were only drug companies. Thai FDA did not include hospitals. Although post-marketing

division arranged the meeting with hospitals 2 times per year, there was no issue related to SMP. All 6 drug companies (100.00%) received SMP guideline from PREMA.

Twelve hospital pharmacists (75.00%) never received SMP guideline from Thai FDA. Only 2 hospital pharmacists (12.50%) experienced attending conference (UH1-ADR pharmacist, UH3-DIS pharmacist) while 2 hospital pharmacists (12.50%) accessed Thai FDA website to obtain SMP guideline by themselves since hospital accreditation (HA) compelled hospital to establish SMP protocol (UH4-OPD pharmacists). All hospital physicians (100.00%) never received SMP guideline.

It indicated that all regulatory authorities and all drug companies were aware of SMP guideline. In contrast, most hospital pharmacists and all hospital physicians were unaware of SMP guideline.

*"I participated in SMP conference set by Thai FDA in 2018. Thai FDA provided information on risk level." (UH1-ADR pharmacist)*



*"I attended online conference on the topic "Black box warning organized by Mahidol University in March 2021. SMP risk-based approach was the sub-topic of the conference provided by pharmacist from Thai FDA. I knew that guideline was changed into new criteria categorized by risk level but it was not clear. I did not understand all contents. It needed time to read the full guideline in order to understand more." (UH3-DIS pharmacist)*

*"I accessed Thai FDA website to obtain SMP guideline because*

*HA forced hospital to create monitoring program for new drugs with SMP. I focused on the criteria for reporting ADR. I did not focus on risk level and I could not remember the details." (UH4-OPD pharmacist)*

*"I never received SMP guideline. I knew SMP term. However, I was not interested." (UH3-Oncologist)*

*"I never received SMP guideline. I never heard about SMP before. This was the first time that I heard from you." (UH1-Oncologist)*

**Understanding of SMP guideline**

Understanding of SMP guideline included clarity of SMP guideline and opinion on SMP risk-based approach

**Clarity of SMP guideline**

Definition of pre-launching was the most ambiguous issue following method of early informing and reminding, method of monitoring new drugs with SMP-risk level 1 and the absence of PV inspection issue.



Definition 1 month before launching

Four drug companies (66.67%) commented that the definition of providing safety information 1 month before launching was vague. It was difficult to interpret timeline to implement the activities whether drug companies could conform to this activity when new drugs with SMP were in process of considering into hospital drugs lists or drug companies must perform these activities at the time of new drugs with SMP which had already been permitted into hospital drugs lists (MNC2,

MNC3, MNC4, DTC2). Regulatory authorities clarified that drug companies could provide safety information to healthcare professionals after approval. Timetable could be flexible (Pre-Thai FDA1 expert, Post-Thai FDA1 director).

Methods of early informing and reminding

Two drug companies (33.33%) commented that it was not articulate about methods of early informing and reminding safety information mentioned in SMP guideline. Drug companies must design by themselves whether it should send letters or only visit by medical representatives or train healthcare professionals (DTC1, DTC2). Pre-marketing regulatory authority expressed that method of reminding should depend on risks of medicinal products. If it was high risk medicinal product, it needed special training for physicians (Pre-Thai FDA1 expert) while post-marketing regulatory authority stated that drug companies could use any methods relying on their opinion (Post-Thai FDA1 director).



Methods of monitoring new drugs with risk level 1

Two drug companies (33.33%) commented that the description of method of active surveillance for new drugs with SMP risk level 1 was in general. It needed to specify more details (MNC1, MNC3). Regulatory authorities clarified that drug companies could conduct cohort event monitoring or patient registry for new drugs with SMP risk level 1 (Pre-Thai FDA1 expert, Post-Thai FDA1 director).

PV inspection

One regulatory authority (16.67%) commented that SMP guideline did not address PV inspection. It was nebulous on punishment if drug companies did not obey the SMP guideline (Post-Thai FDA1 director).

**Opinion on SMP risk-based approach**

Opinion on SMP risk-based approach regarding methods of monitoring and monitoring period was elucidated.

Methods of monitoring new drugs with SMP

All regulatory authorities' perspective was consistent with drug companies' perspective on methods of monitoring new drugs with SMP. SMP guideline obviously addressed types of new drugs for each risk level. Methods of monitoring new drugs with SMP were appropriate according to risks of medicinal products. Previously, all high risk and low risk medicinal products were monitored by using similar method. Currently, new drugs with higher risks were required to conduct active surveillance. It was acceptable that new drugs with SMP risk level 1 approved with clinical trial phase 2 required to perform active vigilance for all cases every visit due to lack of safety data from clinical trial phase 3. However, it was cumbersome to carry out active vigilance because of human resources and financial resources.

*"Previously, both high risk and low risk new drugs were*

*monitored by using the same method. The SMP risk-based was a good approach because the new guideline required that higher risk new drugs needed more intensive monitoring than lower risk new drugs" (Post-Thai FDA1 director)*

*"For risk level 1, phase 3 was not established. Registry was the good mean. Drug company must monitor all cases at every visit. However, it was difficult in real practice. If drug company paid physicians for processing whether it could be conflict of interest. In addition, the proposal was required to be approved by hospital ethic committee. It took time. If drug company hired vendor, the vendor needed minimum requirement such as 50 cases. Drug company could not guarantee whether cases would reach the prerequisite." (MNC2)*

Early informing and reminding

The concept of early informing and reminding was adopted from Japan. The purpose of these new activities was to increase healthcare professionals' awareness to report ADR during the first 6 months after launching (Pre-Thai FDA1 expert). Drug companies agreed with the innovative methods that drug companies must take more actions in reminding, facilitating and encouraging healthcare professionals to report ADR of new drugs with SMP. It anticipated that the number of ADR reports of new drugs with SMP would increase from these activities.



*"Intensified reporting system was the new activity that drug company must frequently remind physicians to report ADR. I personally thought that this new method would alert contact person for PV and medical representatives*

*to concern more about SMP. It was not only waiting for physicians to report ADR to drug company. It was two-way communication. This method was beneficial to maximize number of ADR reports." (DTC1)*

Monitoring period of new drugs with SMP

All 6 regulatory authorities (100.00%) and all 6 drug companies (100.00%) also agreed that the monitoring period was suitable. High risk new drugs with SMP risk level 1 were required to monitor for at least 2 years and new drugs with SMP risk level 2 were requested to monitor for 2 years while low risk new drugs with SMP risk level 3 were desired to monitor for only 1 year.

*"For example, new drugs with risk level 3 were changed from intravenous to subcutaneous. It was unnecessary to monitor 2 years as previously approved drugs because it only changed dosage form. Therefore, it was acceptable that the monitoring period was shorter for risk level 3. New SMP risk-based approach was rationale." (MNC1)*



As above mentioned, all six regulatory authorities and all six drug companies could provide opinion on SMP risk-based approach whereas only 4 hospital pharmacists (25%) reached SMP guideline. Of these, 2 hospital pharmacists attended conference and 2 hospital pharmacists accessed SMP guideline on Thai FDA website. However, only one hospital pharmacist who participated in conference expressed the agreement on SMP guideline whereas other 3 hospital pharmacists could not provide opinion on SMP guideline because they were not interested.

The different perspectives from two pre-marketing regulatory authorities (33.33%) were that SMP should be discontinued and use only RMP because RMP was the tool to ensure benefit-risk of medicinal products throughout the life cycle of a drug (Pre-Thai FDA2, Pre-Thai FDA3).

According to SMP guideline, all regulatory authorities and all drug companies were aware of SMP guideline and they agreed with SMP risk-based approach. However, most hospital pharmacists and all hospital physicians rarely received SMP guideline. The establishing of SMP protocol would reflect the relevant stakeholders' understanding on SMP guideline. It would be detailed in part of the SMP protocol.

**SMP protocol**

The purpose of SMP protocol was to assist relevant stakeholders to carry out risk minimization activities and pharmacovigilance activities. Basically, drug companies had duties to prepare and submit SMP protocol to Thai FDA to approve. Contact person for PV of drug companies was responsible for implementing SMP protocol and coordinating with hospitals.



As aforementioned, all 6 drug companies (100.00%) reached SMP guideline and understood the concept of SMP risk-based approach. Therefore, drug companies enabled to formulate SMP protocol following risk level confirmed by regulatory authorities. Of these 6 drug companies, 5 drug companies (83.33%) had new drugs with SMP risk level 2 preparing SMP protocol using intensified reporting system.

Only 1 drug company (16.67%) had new drugs with SMP risk level 1 (anti-cancer) using registry. Drug companies mainly coordinated with hospital physicians. Medical representatives were responsible for collecting ADR reports from hospital physicians. However, drug companies did not collaborate with the hospital pharmacists regarding SMP protocol because drug companies did not know the focal point of hospital pharmacists.

In contrast, most hospital pharmacists and all hospital physicians never received SMP guideline. Thus, healthcare professionals did not understand the concept of SMP risk-based approach. In addition, they never received SMP protocol from drug companies. Hospital pharmacists established their own SMP protocol because of hospital accreditation institute enforcement. Generally, Pharmacy Therapeutic Committee (PTC) supervised drug management in the hospitals. However, PTC had less role in initiating SMP protocol. DIS/ADR pharmacists were the mainly responsible person in developing SMP protocol.



Five hospitals (62.50%) had SMP protocol for pharmacists. The SMP protocol did not rely on risk level. Hospital pharmacists monitored all high risk and low risk new drugs with SMP by using the similar methods. These hospitals used specific tool that was check lists for ADRs of new drugs with SMP. Of these, 3 hospitals quantified ADRs by pharmacists at dispensing units (UH2, UH3, UH4) whereas 1 hospital identified ADRs by calling patients (UH5) and 1 hospital detected ADRs by calling to physicians (TH1). On the other hand, 3 hospitals (37.50%) had no SMP protocol for

pharmacists. Two hospitals (UH1, TH2) used passive method at dispensing unit while 1 hospital monitored patients in ambulatory clinic (TH3). All hospitals had no SMP protocol for physicians.

It indicated that the collaboration of SMP protocol between drug companies and hospitals were not well established. Drug companies and hospitals had different SMP protocol. The formulating of SMP protocol reflected that drug companies understood the SMP guideline whereas hospital pharmacists had misconceptions of the SMP guideline.

**National database of approved drugs**

The purpose of national database of approved drugs was to facilitate relevant stakeholders to review status of new drugs with SMP. If new drugs were still in SMP, it needed to continue monitoring following SMP protocol. If new drugs were removed from SMP, it would monitor by using regular method.



Pre-marketing regulatory authorities were responsible for updating status of new drugs with SMP whereas post-marketing regulatory authorities could not access internal database. Post-marketing regulatory authorities accessed national database of approved drugs on Thai FDA website to obtain lists of medicinal products registered in Thailand to support in signal assessment. Post-marketing regulatory authorities did not aim to check status of new drugs with SMP. Post-marketing regulatory authorities also commented that there was no risk level of new drugs with SMP on national database of approved drugs. Drug companies did not employ

database of approved drugs. Drug companies knew status of their products. Hospital pharmacists accessed national database of approved drugs to check status of new drugs with SMP.

The hospital pharmacists' opinion on accessibility and convenience of national database of approved drugs was described. Three hospitals (37.50%) enabled to access national database of approved drugs and it was convenient (UH2, UH4, UH5). Three hospitals (37.50%) enabled to access national database of approved drugs but it was inconvenient (UH1, UH3, TH3). Two hospitals (25.00%) were unable to access national database of approved drugs (TH1, TH2).

**Agreement on convenience of national database of approved drugs**

Three hospitals (37.50%) accepted that it was convenient to check status of new drugs with SMP on national database of approved drugs (UH2, UH4, UH5). The reasons for this were that it was comfortable to key in searchable database and easy to understand the status because the outputs of searching presented the obvious wording "within SMP condition or remove from SMP condition" as well as approval date and removal date. As the results of this, UH4 updated lists of new drugs with SMP every month whereas UH2 and UH5 updated lists of new drugs with SMP every year. If new drugs were removed from SMP, UH2 would delete SMP code from hospital database while UH4 and UH5 would erase those new drugs with SMP from google sheet.

*"There was no problem about searchable database. If new drugs were removed from SMP. I would remove the SMP code from hospital database." (UH2-ADR OPD pharmacist)*

*"I checked status for 18 items of new drugs with SMP subject to monitor every month. There was no problem on accessibility of searchable database. It was easy to key and easy to understand. Thai FDA clearly informed status of new drugs with wording "within condition or remove from condition" as well as approval date and removal date. Then, I removed lists from google sheet" (UH4-OPD pharmacist)*

**Disagreement on convenience of national database of approved drugs**

Three hospitals (37.50%) commented that national database of approved drugs for checking status of new drugs with SMP was inconvenient (UH1, UH3, TH3). The elucidation for this was that pharmacists had no time to do this task. In addition, it took time to key each item due to several number of new drugs with SMP. As a consequence of this, UH1 and UH3 did not update lists of new drugs with SMP while TH3 revised lists of new drugs with SMP by requesting drug companies to notify status of new drugs with SMP. Drug companies informed TH3-DIS pharmacists by providing official letter issued from Thai FDA to verify that new drugs were removed from SMP. Then, TH3-DIS pharmacist re-checked the status on national database of approved drugs to ensure that those new drugs were removed from SMP.



*"Normally, I checked status of new drugs with SMP via Thai FDA*

*registration database. However, it was difficult to check whether new drugs were removed from condition for each new drug due to large number of items and took time. I had other tasks to do apart from checking status of new drugs with SMP. Previously, Thai FDA used to provide the updated lists of new drugs with SMP in PDF file upload on website. However, I did not see this document for a long time. I could not remember which website to search this information" (UH1-DIS pharmacist)*

*"Method for checking status of new drugs with SMP was that I must key registration number of each new drug into searchable database. However, there was no revision of the lists of new drugs with SMP because there was no time to check each new drug. I had a lot of work. There was no complete file to check status." (UH3-DIS pharmacist)*

*"Normally, I checked status of new drugs with SMP via searchable database at the time of new drugs with SMP entering into hospital. However, I did not check status whether new drugs were removed from SMP. The reason for this was that I had a lot of work. I did not focus on this task. The easy way was that I told drug companies to inform when their products were removed from SMP." (TH3-DIS pharmacist)*



**Un-accessibility of national database of approved drugs**

Two hospitals (25.00%) were unable to access national database of approved drugs (TH1, TH2). They used to check status of new drugs with SMP with line listing in PDF file. However, they could not find the update lists of new drugs with SMP

in PDF file after 2019 on Thai FDA website. As a consequence of this, TH2-DIS pharmacist could not establish lists of new drugs with SMP. For TH1, there was the existing lists of new drugs with SMP, but TH1-DIS pharmacist was unable to update the status of new drugs with SMP.

It indicated that national database of approved drugs was difficult to access and it was inconvenient. As a consequence of this, it was the influencing factors related to the existing lists of new drugs with SMP that would be explained in the subsequent topic.

**The existing lists of new drugs with SMP**

The purpose of the existing lists of new drugs with SMP was to inform relevant stakeholders regarding risk level for each new drug with SMP to monitor.

At Thai FDA, the line listing of new drugs with SMP for each risk level was not available. Only pre-marketing regulatory authorities knew risk level because they were responsible for approving new drugs with SMP whereas post-marketing regulatory authorities did not know risk level for each new drug with SMP because there was no communication of lists of new drugs with SMP from pre-marketing division to post-marketing division.



All 6 drug companies (100.00%) knew risk level of their medicinal products. Five drug companies (83.33%) had new drugs with SMP risk level 2 whereas one drug company (16.67%) had new drugs with SMP risk level 1 and risk level 2 (MNC1).

At hospital level, 6 hospitals (75.00%) had the existing lists of new drugs with SMP. However, the SMP lists were not categorized according to risks of medicinal products because hospitals did not know risk level for each new drug. On the other hand, 2 hospitals (25.00%) had no lists of new drugs with SMP. The reason for this was that national database of approved drugs was inconvenient to check status of new drugs with SMP.

It indicated that there was no existing list of new drugs with SMP for each risk level to support relevant stakeholders. Only pre-marketing regulatory authorities and drug companies knew risk level for each new drug with SMP while post-marketing regulatory authorities and healthcare professionals in the hospitals did not know risk level for each new drug with SMP.

**Dissemination of lists of new drugs with SMP within hospitals**

Five hospitals (62.50%) disseminated lists of new drugs with SMP within hospitals. Two hospitals (UH2, UH4) distributed on hospital intranet, 2 hospitals (UH3, UH5) conveyed on hospital website while 1 hospital communicated via hospital pharmacy Line group (TH1). Furthermore, 2 hospitals also labelled SMP symbol on stickers and prescriptions to notify pharmacists at dispensing units as well as alerted SMP notification on hospital program to inform physicians (UH2 and UH3) whereas 1 hospital also displayed SMP symbol on drugs shelves at pharmacy station (UH4). All pharmacists in these 5 hospitals affirmed that they reached the existing lists of new

drugs with SMP while all hospital physicians did not know channels to access lists of new drugs with SMP.

On the other hand, 3 hospitals (37.50%) did not circulate new drugs with SMP within hospitals. The reason for this was that 2 hospitals had no lists of new drugs with SMP (UH1, TH2) whereas 1 hospital mentioned that it was unnecessary to disseminate lists of new drugs with SMP because this hospital monitored all drugs by using regular method (TH3).

**Processes of SMP**

Processes of SMP comprised distribution of safety information, methods of monitoring new drugs with SMP for drug companies and hospitals, ADR reporting to Thai FDA, risk assessment and risk communication.

**Distribution of safety information**

The purpose of distribution of safety information of new drugs with SMP was to underpin important ADRs to relevant stakeholders to monitor. Timetable of early informing and reminding, methods of early informing and reminding, awareness of important ADR and usability of safety information were elucidated in table 26.

**Timetable of early informing and reminding**

The purpose of early informing and reminding was to increase healthcare professionals' compliance in ADR reporting.

Early informing (Pre-launching)

All 6 drug companies (100.00%) asserted that they followed SMP guideline by providing safety information 1 month before launching. All hospital physicians (100.00%) confirmed that they received safety information before new drugs launched into hospitals from drug companies.

Reminding (Post-launching)

All 6 drug companies (100.00%) affirmed that they reminded physicians every 2 months in the first 6 months following SMP guideline. At month 8, drug companies sent the document of reminding to Thai FDA to report that drug companies complied the activities. All hospital physicians (100.00%) also confirmed that they periodically received reminding on safety information from drug companies.

Follow-up the compliance of drug companies

Regulatory authorities confirmed that they received recorded documents of early informing and reminding from drug companies. However, regulatory authorities did not ensure the compliance of drug companies in real practice because there was no PV inspection.

*"Although drug companies sent recorded document to confirm that they early informed and reminded healthcare professionals. However, it was curious whether drug companies did these activities in real practice." (Pre-Thai FDA1 expert)*

*"Drug companies usually sent the progression of activities. However, it could not confirm whether these drug companies processed the activities in real practice. There was no consensus which division should have duty to follow-up the compliance of drug companies." (Pre-Thai FDA2)*

**Methods of early informing and reminding for new drugs with SMP**

Major method of early informing and reminding safety information in all 6 drug companies (100.00%) were visiting physicians by medical representatives. However, drug companies could not confirm whether medical representatives visited and reminded physicians. Therefore, 2 drug companies (33.33%) also used additional methods to complement visiting by medical representatives (MNC2, MNC4). MNC2 sent letters via post to heads of physicians while MNC4 sent e-mail to operational physicians. For sending via post, MNC2 received tracking number of letters in order to record in reminding form to assert that drug companies complied with these activities. The letter was the formal way to notify physicians. MNC2 expected that the letters would be distributed within hospitals. However, it could not affirm whether the letters reached all targeted audiences. For sending e-mail, MNC4 had the lists of hospital physicians to send via e-mail. It was convenient way to circulate. All hospital physicians (100.00%) confirmed that they received early informing and reminding by medical representatives. However, all hospital physicians never received information via letter or e-mail.

**Awareness of importance ADR**

Safety materials from drug companies

All 6 drug companies (100.00%) basically provided PIL as routine risk minimization activities for all medicinal products and educational materials as additional risk minimization activities for some medicinal products. All hospital pharmacists (100.00%) and all hospital physicians (100.00%) confirmed that they received this information.

Opinion on ADR information were consistent among hospital pharmacists that drug companies provided the whole information. Hospital pharmacists must extract only significant ADRs to prepare check lists by themselves. Hospital physicians mentioned that drug companies mainly focused on efficacy. This implied that important ADRs were less emphasized.

Safety materials from Thai FDA



There was no available ADR information including PIL or educational material upload on Thai FDA website. Post-marketing regulatory authorities requested database to support information on PIL so that they could check known ADR and unknown ADR in the process of signal detection and signal assessment.

The available ADR information from post-marketing division was the summary of annual ADR reports of Thai population from 1984 to present on HPVC website with basic information including medicinal products' name in generic,

adverse events, frequency and causality. However, hospital pharmacists and hospital physicians never reached those data.

**Usability of safety information**

The above mentioned, ADR information was not readily available to be used. Hospital pharmacists must provision check lists for ADRs of new drugs with SMP by themselves. Six hospitals (75.00%) produced check lists for ADRs of new drugs with SMP for pharmacists whereas 2 hospitals (25.00%) had no check lists for ADRs of new drugs with SMP (UH1, TH2). All hospital had no check lists for ADRs of new drugs with SMP for physicians.

Basically, all hospital pharmacists used PIL as a source of ADR information. Moreover, 3 hospitals also searched other sources (UH3, UH5, TH3). UH3 accessed Lexicom online because it provided the frequency in percentage of ADRs whereas UH5 reviewed ADRs of new drugs with SMP from articles in order to know timeline of the occurrence of ADRs in order to specify timetable to follow-up patients. TH3 also prepared check lists for ADRs in oncology ambulatory care clinic from standard guideline of cancer. Furthermore, 2 hospitals suggested that Thai FDA should provide check lists for significant ADR information of new drugs with SMP to monitor (UH2, TH2).



*"I prepared lists for ADRs of new drugs with SMP by extracting ADR information from leaflet. Drug companies provided the whole information. Thai FDA should provide ADR information of new drugs with SMP to monitor categorized by*

*therapeutic group. It would be convenient for pharmacists." (UH2-ADR OPD pharmacist)*

*"I searched another source such as Lexicom online for preparing check lists for ADRs of new drugs with SMP because this source provided the frequency in percentage of ADR (<1%, <10% or >10%). I selected ADR with more than 10% first and also chose significantly rare ADR." (UH3-DIS pharmacist)*

*"Apart from PIL, we reviewed ADRs of 2 new drugs with SMP subject to monitor from articles in order to know onset of ADR. We found that ADRs of 2 new drugs with SMP usually appeared during 6-8 weeks after using medicines. Therefore, we must intensively monitor during this period" (UH5-ADR pharmacist)*

*"There was no tool to help operational pharmacists to identify ADRs of new drugs with SMP. Drug companies provided a whole lot of safety information. Thai FDA should provide the important ADR information to monitor such as 5 significant ADRs. This would be the standard information for all hospitals." (TH2-DIS pharmacists)*



All hospital pharmacists and all hospital physicians have awareness of safety information. However, safety information was not readily to be used. Hospital pharmacists must extract prominent ADR by themselves in order to establish check lists for ADRs.

**Methods of monitoring new drugs with SMP: Drug companies**

The components of methods of monitoring new drugs with SMP for drug companies included routes of ADR reporting from physicians to drug companies, routes of ADR reporting from medical representatives to contact person for PV at drug companies, method of monitoring new drugs with SMP risk level 1 and causality assessment. Summaries of methods of monitoring new drugs with SMP for drug companies were illustrated in table 27.

**Routes of ADR reporting from physicians to drug companies**

Medical representatives notified routes of ADR reporting to drug companies for hospital physicians including ADR form paper-based, a verbal informing to medical representatives or phoning to call center. Physicians mentioned that they verbally informed ADRs to medical representatives.

Drug companies stated that medical representatives also requested ADR reports of new drugs with SMP from hospital physicians. Drug companies commented that they received low number of ADR reports of new drugs with SMP from hospital physicians. However, hospital physicians stated that medical representative rarely requested ADR reports from them. Hospital physicians rarely reported ADR to drug companies because of no serious ADR and confidential information.

**Routes of ADR reporting from medical representatives to contact person for PV at drug companies**

Routes of ADR reporting from medical representatives to contact person for PV at drug companies included ADR form paper-based, telephone or e-mail, and drug companies' application. Two drug companies (33.33%) used ADR form (MNC4, DTC1). Two drug companies (33.33%) employed telephone or e-mail (MNC1, DTC2). Two drug companies (33.33%) exploited drug companies' application (MNC2, MNC3). The disadvantage of ADR form paper-based was that it was difficult to read handwriting whereas drug companies' application was convenient because ADR information was automatically entered into drug companies' database. E-mail and telephone were also comfortable.

*"Medical representatives previously reported ADR to contact person for PV at drug companies via telephone and e-mail. Later, drug company developed program to report ADR within organization in January 2021 in order to have a lean system. It was more comfortable than conventional route. Medical representatives could fill in mandatory box" (MNC2).*



**Method of monitoring new drugs with SMP risk level 1**

One drug company (16.67%) had only one new drug with SMP risk level 1 to monitor using manual registry (MNC1). That drug company enabled to monitor all cases because of small number of patients. However, the problem was that if medical representatives were changed, data would be lost. Drug company could not follow-

up information from physicians. Drug company received information only from medical representatives.

*"Drug company had only one new drug with SMP risk level 1. It was anti-cancer with high price. Drug company used manual method to collect data. Medical representatives recorded number of patients each month for each visit. Drug company could monitor all patients due to low number of patients." (MNC1)*

**Causality assessment**

One drug company (16.67%) processed causality assessment in term of related or un-related between ADRs and suspected drugs (MNC1). Then, MNC1 reported as un-classified if ADR reports were un-related to Thai FDA whereas causality assessment in 5 drug companies (83.33%) was globally operated.

Overall, all drug companies obtained low number of ADR reports of new drugs with SMP from healthcare professionals. Although drug companies confirmed that they operated early informing and reminding as well as implemented SMP protocol following risk level, Thai FDA could not ensure whether drug companies complied with these activities in real practice due to lack of PV inspection.



**Methods of monitoring new drugs with SMP: Hospitals**

Hospital physicians and hospital pharmacists carried out actual action for risk minimization activities and pharmacovigilance activities following their own protocol. Methods of monitoring new drugs with SMP at hospital level were explained according to physicians' role and pharmacists' role. It included risk minimization activities and

pharmacovigilance activities. The purpose of risk minimization activities was to reduce and prevent serious ADR. The components of risk minimization activities comprised compliance on pre-prescribing for new cases and routine follow-up, compliance on ADR management and compliance on ADR counselling. The aim of pharmacovigilance activities was to identify ADRs. The elements of pharmacovigilance activities consisted of identifying methods, timetable to follow-up, causality assessment, types of ADR report, and number of ADR reports. Summaries of method of monitoring new drugs with SMP for hospitals were presented in table 28.

**Physicians' role**

Physicians processed risk minimization activities and pharmacovigilance activities for all types of medicinal products by using similar methods. There was no SMP protocol for physicians.

**Risk minimization activities: Physicians' role**



Compliance on pre-prescribing for new cases and routine follow-up, and compliance on ADR management was elaborated.

<u>Compliance on pre-prescribing for new cases and routine follow-up</u>

Physicians checked patient's history of drug allergy, contraindication and monitored specific laboratory for new drugs.

*"For new cases, I checked patients' history of drug allergy, contraindication for liver function, kidney function and checked drug interaction before prescribing. In addition, patients were provided education for basic*

*management of ADR. Furthermore, I routinely monitored CBC, liver function test or EKG." (UH1-Oncologist)*

Compliance on ADR management

The options for ADR management included medicine continuation, temporary discontinuation and permanent discontinuation. As for the results, there was no serious ADR. Physicians could prevent and mitigate risk of new drugs.

*"If ADR occurred, I managed following guideline. If patient developed from grade1 diarrhea to grade2 diarrhea. I had to adjust dose and advised before progressing to moderate and severe diarrhea." (UH1-Oncologist)*

*"For example, proteinuria from anti-cancer. I discontinued medication and monitored until proteinuria recovered to grade1 and re-started medication." (UH3-Oncologist2)*



*"If there was necrosis of jaw from anti-cancer. I permanently discontinued this medication and shifted to other groups. (UH3-Oncologist1)*

**Pharmacovigilance activities: Physicians' role**

The elements of pharmacovigilance activities consisted of identifying method, timetable to follow-up, causality assessment, types of ADR reports to pharmacists and route of ADR reporting from physician to pharmacist.

Physicians identified by asking about important ADRs. There was no

check list for ADRs of new drugs with SMP for physicians. Physicians monitored all patients every visit in routine follow-up. The difficult issues of causality assessment were co-medications and co-diseases. Normally, physicians reported drug allergy-type B ADR and serious-type A ADR to pharmacists. Physicians did not report non-serious ADR due to manageability.

*"I never reported non-serious side effect to pharmacists. I reported only drug allergy. For non-serious side effect, I recorded in EMR and addressed that it was mild grade and advised to patients. It was manageable." (UH1-Oncologist)*

Route of ADR reporting from physician to pharmacist, physicians in 4 hospitals (50.00%) could inform ADRs via paper note (UH5, TH1, TH2, TH3) while physicians in 3 hospitals (37.50%) could inform ADRs via hospital online program and paper note (UH1, UH2, UH4). In one hospital (12.50%), physicians could report ADR via hospital website (UH3). As the results, 7 physicians (87.50%) informed ADR to pharmacists by taking note on prescription. One physician (12.50%) informed ADR to pharmacist by telephone calling.



**Pharmacists' role**

Five hospitals (62.40%) had SMP protocol for pharmacists (UH2, UH3, UH4, UH5, TH1). These hospitals had a significant tool that was check lists for ADRs of new drugs with SMP. On the other hand, 3 hospitals (37.50%) had no SMP protocol (UH1, TH2, TH3). Only TH3 had check lists for ADRs in oncology ambulatory care clinic

whereas UH1 and TH2 had no check list for ADRs of new drugs with SMP. These 2 hospitals used passive method.

For items of new drugs with SMP subject to monitor, 3 hospitals (37.50%) selected some items to monitor. UH4 and UH5 selected 18 items and 2 items from 100 items to monitor, respectively. These 2 hospitals selected small items of new drugs with SMP to monitor because pharmacists aimed to follow-up all cases and every visit according to their abilities whereas UH3 selected 60 items from 100 items depending on serious ADRs. However, the criteria for selecting targeted new drugs with SMP to monitor was not considered on risk level. In contrast, other 5 hospitals (62.50%) monitored all items of new drugs with SMP.

Methods of monitoring new drugs with SMP for pharmacists were described into two parts including risk minimization activities and pharmacovigilance activities. Pharmacists' role on risk minimization activities was focused on counselling for new cases by providing common ADR to new patients. For routine follow-up, pharmacists emphasized on pharmacovigilance activities.



**Risk minimization activities: Pharmacists' role**

Pharmacists' role on risk minimization activities was to provide common ADRs of new drugs with SMP to new patients to recognize. Two hospitals (25.00%) advised common ADR to new patients (UH4, TH3) while 6 hospitals (75.00%) did not inform ADRs to new patients. Operational pharmacists provided regular counselling.

**Pharmacovigilance activities: Pharmacists' role**

Pharmacists' role on pharmacovigilance activities were categorized into 2 groups. Group 1 was hospitals with SMP protocol. Group 2 was hospitals without SMP protocol.

**Group 1: SMP protocol**

Five hospitals had SMP protocol. It was classified into 2 groups relying on responsible pharmacists. Three hospitals processed by operational pharmacists at dispensing units (UH2, UH3, UH4) while 2 hospitals, ADR/DIS pharmacist operated by phoning to patients (UH5) and calling to physicians (TH1).

**Operational pharmacists at dispensing unit**

UH2, UH3 and UH4 monitored and quantified ADRs of new drugs with SMP by operational pharmacists at dispensing unit. Identifying methods were different among 3 hospitals. UH2, UH3 and UH4 used paper-note, hospital website and scan QR code on check lists for ADRs of new drugs with SMP, respectively. The processes of pharmacovigilance activities of each hospital were described and then followed by comparing among hospitals.



<u>The description of processes of pharmacovigilance activities</u>

UH2 monitored all 74 items of new drugs with SMP in hospital. SMP symbol was labelled on stickers and prescriptions to alert operational pharmacists at dispensing unit. UH2 identified ADRs by using paper-note. However, there was no

list of ADR in paper-note. Pharmacists could check with the manual lists of ADR. Then, pharmacists transferred ADR information from paper-note into Excel file and followed by filling in HPVC form. UH2 planned to follow-up patients every visit. As a consequence of this method, there was low ADR reports of new drugs with SMP in the previous year.

UH3 selected 60 items of new drugs with SMP from 100 items to monitor. The criteria for selecting depended on serious ADRs. SMP symbol was addressed on stickers and prescriptions to notify operational pharmacists at dispensing unit. UH3 detected ADRs by employing check lists for ADRs of new drugs with SMP via hospital website. ADR data of new drugs with SMP were automatically recorded into google sheet. Operational pharmacists were also required to record both ADR cases and non-ADR cases in order to confirm that they did this task. Then, UH3-DIS pharmacist filled in HPVC form following ADR information in Google sheet. UH3 planned to follow-up patients every visit. As the results of this method, there were 50 cases of ADR of new drugs with SMP in the previous year.



UH4 selected 18 items from 100 items of new drugs with SMP to intensively monitor. Criteria of choosing included 1 item for each dispensing unit, severity and usage rate. In addition, there was SMP symbol on drug shelves to notify operational pharmacists at dispensing unit. Operational pharmacists identified ADR by scanning QR code to check with lists for ADR of new drugs with SMP and submitted reports into google sheet. UH4 planned to follow-up patients every visit. As the results

of this method, there were 100 cases of ADR of new drugs with SMP per month in the previous 3 months (January 2021 to March 2021).

Comparison of processes of pharmacovigilance activities

Pharmacovigilance activities of new drugs with SMP of UH2, UH3, and UH4 were compared following these components: identifying methods, timetable to follow-up, causality assessment, types of ADR report, and number of ADR reports.

Identifying methods

UH3 and UH4 identified and recorded ADR of new drugs with SMP via hospital website and scanned QR code, respectively. It was convenient since data were automatically entered into Google sheet. On the other hand, UH2 recorded ADRs of new drugs with SMP on paper note. The problem was that data were not automatically filed into database in real time. Operational pharmacists manually documented in Excel file and followed by filling in HPVC form. Therefore, it wasted time to manage data because of complicated steps.



Timetable to follow-up

UH2, UH3 and UH4 anticipated to follow-up patients every visit. UH4 operational pharmacists confirmed that they identified ADRs of new drugs with SMP every visit when they dispensed for all patients receiving targeted new drugs with SMP subject to monitor. UH4 could monitor all patients every visit because UH4 chose only 18 items from 100 items of new drugs with SMP in order to monitor according to their abilities. On the other hand, UH2 and UH3 could not monitor all

patients every visit due to several items of new drugs with SMP and several patients receiving new drugs with SMP. UH2 monitored all 74 items whereas UH3 monitored 60 items from 100 items. Therefore, items of new drugs with SMP were important factors influencing timetable to follow-up.

Causality assessment

The difficult issues of causality assessment were co-medications and unclear timeline (UH2, UH3). UH4 did not assess causality of ADR. UH4 only identified following check lists for ADRs. Therefore, it could not confirm whether ADR was related to suspected new drugs.

Types of ADR report

UH2, UH3 and UH4 reported all types of ADR.

Number of ADR report of new drugs with SMP

UH2 obtained low ADR reports from 74 items of new drugs with SMP. UH3 gathered 50 ADR reports in the previous year from 60 items of new drugs with SMP. UH4 collected 100 ADR reports per month from 18 items of new drugs with SMP.



**ADR/DIS pharmacists at ADR/DIS center**

UH5-ADR pharmacists and TH1-DIS pharmacists were mainly responsible persons for pharmacovigilance activities of new drugs with SMP. UH5-ADR pharmacists identified ADRs of new drugs with SMP by calling to patients while TH1-DIS pharmacist detected ADRs of new drugs with SMP by phoning to physicians. The

processes of pharmacovigilance activities of each hospital were described and then followed by comparing between the two hospitals.

The description of processes of pharmacovigilance activities

UH5 selected 2 items from 100 items of new drugs with SMP. Criteria of choosing new drugs with SMP included usage rate, severity, and price. Primary responsible persons were 11 pharmacists at ADR center. There were 2 phases including intensive phase and routine follow-up. For the first phase, ADR pharmacists followed patients via telephone call during intensive period (e.g.in the first 2 months after initiating medications). Then, pharmacists reviewed OPD card every visit for routine follow-up. ADR pharmacists detected ADR following paper check lists. SMP manager had duties to obtain lists of patients receiving targeted new drugs with SMP from hospital database once a week and assigned to each pharmacist in ADR team. The data were collected in Google sheet and then filled in HPVC form. As the results of this method, there were 23 cases of ADR of new drugs with SMP in the previous 6 months (October 2020 to March 2021).



TH1 monitored all 4 items of new drugs with SMP in hospital. DIS pharmacist called to physicians every 6 months in order to identify ADRs of new drugs with SMP following check lists for ADRs. In addition, TH1-DIS pharmacist also reviewed patients' history regarding ADRs in hospital database. Physicians replied by verbal within 1 or 2 days. If physicians did not respond, TH1-DIS pharmacist would

remind them. Then, TH1-DIS pharmacists recorded data in Excel file. There was low number of ADR reports of SMP in the previous year.

Comparison of processes of pharmacovigilance activities

Pharmacovigilance activities for new drugs with SMP between UH5 and TH1 were compared following these topics: identifying methods, timetable to follow-up, causality assessment, types of ADR report and number of ADR reports.

Identifying methods

There was no problem for UH5-ADR pharmacist in identifying ADR by calling to patients in intensive phase and reviewing OPD card in routine phase. TH1-DIS pharmacist also had no problem in detecting ADR by phoning to physicians. For data record, UH5-ADR pharmacists and TH1-DIS pharmacist recorded data on Google drive and Excel file, respectively. It was convenient.

Timetable to follow-up



UH5 could follow-up all patients every visit. The explanations for this were elaborated. First, UH5 selected only 2 items from 100 items of new drugs with SMP to intensively monitor according to their competency. Second, there was clear timetable to gather patients' information for each visit by SMP manager pharmacist once a week from hospital database. Third, there was pre-defined time for calling to patients and reviewing OPD card according to SMP protocol. TH1 monitored

all 4 items and was able to follow-up all cases due to small number of patients receiving new drugs with SMP.

Causality assessment

UH5-ADR pharmacists phoned to patients for identifying ADR. However, it lacked diagnosis from physicians to confirm. On the other hand, TH1-DIS pharmacist had no problem about causality assessment.

*"Only ADR pharmacists were responsible for monitoring ADR of new drugs with SMP. The difficult issue was diagnosis. I could not make decision only one. It needed to cooperate with physicians." (UH5-ADR pharmacist)*

Types of ADR report

UH5 and TH1 reported all types of ADR.

Number of ADR reports of new drugs with SMP



UH5 obtained 23 ADR reports in the previous 6 months from 2 items of new drugs with SMP. TH1 gathered low ADR reports in the previous year from 4 items of new drugs with SMP.

**Group 2: Without SMP protocol**

Three hospitals had no SMP protocol. UH1 and TH2 monitored new drugs with SMP by using passive method while TH3 monitored new drugs with SMP in ambulatory care clinic. Pharmacovigilance activities of UH1, TH2 and TH3 were

compared by the following topics: identifying methods, timetable to follow-up, causality assessment, types of ADR report and number of ADR reports.

Identifying methods

UH1, TH2 used passive method to monitor new drugs with SMP. There was no checklist for ADR of new drugs with SMP whereas TH3 had check lists for ADRs of new drugs with SMP in ambulatory care clinic. Operational pharmacists and ambulatory care pharmacists reported ADR to DIS/ADR pharmacists via HPVC form.

*"I could not record all ADR information at the time of dispensing due to a lot of patients. I must retrospectively record. It increased workload. I needed user-friendly program to record while I was talking with patients." (TH2-OPD pharmacist)*

Timetable to follow-up

UH1 and UH2 had no timetable to follow-up while TH3 routinely followed-up patients at ambulatory care clinic.



Causality assessment

The difficult issues were co-medications (UH1, TH2, TH3), unclear timeline (TH2, TH3) and co-diseases (TH3).

Types of ADR report

UH1 and TH2 reported all types of ADR whereas TH3 reported only drug allergy-type B ADRs and serious-type A ADRs.

Number of ADR report of new drugs with SMP

UH1 and TH3 had low ADR report of new drugs with SMP in the previous year whereas TH2 could not specify which ADR reports belonged to SMP.

According to pharmacovigilance activities at hospital level, there was low number of ADR reports of new drugs with SMP in most hospitals. Of these 8 hospitals, 2 hospitals could follow-up all patients every visit due to selection of some items of new drugs with SMP to monitor and obtained high number ADR reports of new drugs with SMP. Two hospitals could not follow-up all patients every visit due to several items of new drugs with SMP and several patients receiving new drugs with SMP to monitor. Thus, they gathered low number of ADR reports of new drugs with SMP. One hospital could monitor all patients due to small number of new drugs with SMP and collected low number of ADR reports of new drugs with SMP. On the other hand, 3 hospitals had no SMP protocol. These hospitals monitored all medicinal products using regular methods. They collected low number of ADR reports of new drugs with SMP. For risk minimization activities, there was no serious ADR. Healthcare professionals could prevent and mitigate ADRs.



**ADR reporting from drug companies and hospital to Thai FDA**

The components of ADR reporting comprised responsible person for ADR reporting, completeness of ADR reports, types of ADR reports, time to report ADR, route of ADR reporting and number of ADR reports of new drugs with SMP. Summaries of ADR reporting were shown in table 29

**Responsible person for ADR reporting to Thai FDA**

At drug companies, contact person for PV were responsible for ADR reporting to Thai FDA. Five hospitals (62.50%) assigned pharmacists to manage and report ADR at ADR/DIS center separately from dispensing unit (UH1, UH3, UH5, TH2, TH3). Two hospitals (25.00%) appointed OPD and IPD representative pharmacists to report ADRs to Thai FDA (UH2, UH4). It meant that these pharmacists were responsible for routine work and ADR reporting. For UH2, OPD and IPD representative pharmacists did not have specified time to report ADR. It depended on the availability from routine work. On the other hand, UH4 assigned 2 OPD pharmacists to separately report ADRs of new drugs with SMP from other non-SMP drugs. They had defined time to prepare and report ADRs of new drugs with SMP to Thai FDA for 2 hours once a week apart from routine work. One hospital (12.50%), DIS pharmacist was designed to report only ADRs of new drugs with SMP while OPD and IPD representative pharmacists in this hospital had obligation to report ADRs of non-SMP drugs (TH1). It indicated that 2 hospitals including UH4 and TH1 emphasized on the importance of responsible person for ADR reporting of new drugs with SMP to Thai FDA.



**Completeness of ADR reports**

Post-marketing regulatory authorities confirmed that the compliance of drug companies and hospitals was good in reporting complete ADR reports with 4 minimum basic information including patients' details, drugs' details, adverse events' details and reporters' details. The score of completeness ranged from grade 0 (low) to

3 (high). Mostly, ADR reports were complete with grade 0 and 1. All 8 hospitals (100.00%) could complete ADR information before sending to Thai FDA. Five drug companies (83.33%) mentioned that ADR information was complete before reporting to Thai FDA except for one drug company (16.67%) (MNC1). Route of ADR reporting from medical representatives to contact person for PV at drug companies was the influencing determinant associated with completeness of ADR information. For drug companies' application (MNC2, MNC3), ADR reports with basic information were automatically entered into drug companies' database. For paper based, 2 drug companies (MNC4, DTC1) had additional strategies to complete ADR information. MNC4 stated that PV person highlighted basic information in ADR form. Therefore, medical representatives could fill in all basic information whereas DTC1 could complete ADR information because physicians signed in consent form to allow drug company to follow-up ADR information. In contrast, MNC1 mentioned that information was approximately complete 50%. Mostly, it lacked age/gender, and lot number of biologic products. Drug company could not follow-up these data from physicians because physicians had no time to provide information.



**Types of ADR report**

The purpose of reporting all types of ADR was in order to know frequency and severity to compare with data from clinical trial whether there was unusual frequency or unknown ADR.

All 6 drug companies (100.00%) reported all types of ADR as well as

7 hospitals (87.50%). Only 1 hospital (12.50%), TH3 reported only drug allergy-type B ADRs and serious-type A ADRs but this hospital did not report non-serious type A ADRs because Thai FDA informed hospitals to report only serious ADRs.

Post-marketing division mandated drug companies to submit both serious and non-serious ADRs. For hospitals, post-marketing division requested only serious ADRs. For non-serious ADRs, it depended on whether hospitals had time to collect. Post-marketing regulatory authorities confirmed that the compliance of drug companies and hospitals was good in reporting both serious and non-serious ADRs.

**Time to report ADR**

All 6 drug companies (100.00%) reported ADR following timetable and 7 hospitals (87.50%) reported ADR of new drugs with SMP within 1 month except for 1 hospital (12.50%). UH3 reported ADR to Thai FDA every 3 months because it had inadequate staff. There was only one DIS pharmacist responsible for ADR reporting and she had several other workloads. According to timetable to submit ADRs, it required to report fatal cases within 24 hours, serious ADR within 15 days and non-serious ADR within 60 days. For the results, there were only non-serious ADRs. It indicated that the compliance of drug companies and hospitals was good in reporting following the timetable.



**Routes of ADR reporting to Thai FDA**

Routes of ADR reporting to Thai FDA included website, post and e-

mail. Post-marketing regulatory authorities stated that website was the most convenient route to gather ADR reporting from drug companies and hospitals because ADR reports were automatically recorded into database. However, if hospitals reported via post and e-mail, post-marketing division was also willing to receive and perceived that the hospitals had huge workload. Post-marketing division had staff to manually enter information into database. All 6 drug companies (100.00%) reported via website as well as 5 hospitals (62.50%) whereas 2 hospitals (25.00%) and 1 hospital (12.50%) reported via post and e-mail, respectively.

**HPVC website**

All 6 drug companies (100.00%) and 5 hospitals (62.50%) (UH1, UH2, TH1, TH2, TH3) reported ADR via HPVC website.

The advantages of HPVC website

From regulatory authorities' perspective, it was convenient to receive ADR reports via HPVC website because the data were automatically entered into database.



From drug companies' perspectives, the advantages of new HPVC website included ADR terms could be solved due to use MedDRA system. Those were the similar terms for both drug company and Thai FDA (MNC1). Moreover, it ensured that ADR information was entered into database (MNC2). Furthermore, it was convenient to update information in case of follow-up via website by entering HPVC

number (DCT1). There was no problem of new HPVC website which compared to the former HPVC website that frequently had errors (MNC3).

From hospital pharmacists' perspectives, pharmacists could fill in ADR information when off-line (UH2, TH1, TH2). New website allowed only ADR report with basic information could be submitted (TH1, TH2). It was also convenient to check whether ADR information was complete before submitting due to only one page of PDF form (TH2). It ensured that ADR reports were entered into national database of ADR reports (TH3). New website provided box to fill in co-incidence or pseudo-allergy assisting pharmacist to easily make decision (UH1). Moreover, it reduced process of sending paper (TH3).

The disadvantages of HPVC website

Post-marketing regulatory authorities obtained the problems of HPVC website from hospitals survey. There was the complaint about download and upload PDF file for route of ADR reporting via HPVC website. From post-marketing regulatory authorities' perspectives, there was no identification of SMP in route of ADR reporting via HPVC website.

From hospitals' perspective, there was no identification of SMP (UH1, TH2). Thai FDA should generate extra menu in order to notify and encourage pharmacist to report ADRs of new drugs with SMP (UH1). In addition, it was difficult to key ICD 10 and ADR terms (UH2, TH1).

From drug company's perspective, only 1 drug company

commented that it was difficult to fill in ADR term in new website. ADR term keyed by reporter did not align with ADR terms in database (MNC4).

*"It was good if there was SMP code. However, it was burden to fill in former data." (Post-Thai FDA2).*

*"There was no fill box for SMP. Thai FDA should provide special menu for ADR reporting of new drugs with SMP to alert pharmacist." (UH1-ADR pharmacist)*

*"It was difficult to key diagnosis, ICD-10 and ADR terms. It took time to search this information. It needed to automatically link data from hospital to Thai FDA." (TH1-OPD pharmacist)*

Feedback from Thai FDA for completeness of ADR reports via HPVC website

For the results of ADR reporting via HPVC website, only ADR report with minimum basic information was allowed to submit into database. Of these 5 hospitals, 3 hospitals received feedback from Thai FDA via letter (UH1, UH2, TH3). ADR information was complete with grade 2 for UH1. ADR information was complete with grade 1 and grade 2 for UH2. ADR information was good grade for TH3. In contrast, 2 hospitals did not receive feedback from Thai FDA (TH1, TH2). TH2-DIS pharmacist accessed HPVC website by herself to check the completeness and found that ADR reports were grade 2. For drug companies, completeness of ADR reports ranged from grade 0-2.

**Post**

Two hospitals (25.00%) reported ADR via post because it was comfortable (UH3, UH5). They were unable to fill in HPVC website since there were several ADR reports including SMP and non-SMP (UH3, UH5) and internet was not available for all computers (UH5). As a consequence of ADR reporting via post, UH3 received feedback from Thai FDA that grade of ADR report was unsatisfactory while UH5 mentioned that there was no feedback about incomplete ADR information from Thai FDA.

*"I selected sending via post. The reason for this was that I could not key online in time due to a lot of ADR reports including SMP and non-SMP." (UH3-DIS pharmacist)*

*"We sent ADR report via post 100%. We were unable to key information via HPVC website. There were large amounts of ADR reports per month including SMP and non-SMP, approximately 100 cases. In addition, internet was not available for all computers." (UH5-ADR pharmacist)*

*"ADR grade was poor due to delay in reporting. I could not remember grade. I received this document once a year. I was not sure how frequently Thai FDA sent to hospital." (UH3-DIS pharmacist)*

*"In the past year, I never received letter sent from Thai FDA to inform the completeness of ADR reports." (UH5-ADR pharmacist)*

**E-mail**

One hospital (12.50%) reported ADR via e-mail (UH4). The explanation for this was that UH4 collected ADR reports by scanning QR code and filling data in Google sheet. Therefore, it was convenient by sending Excel file via e-mail. Pharmacists also informed in e-mail that these ADR reports were SMP. UH4 was unable to report via HPVC website because there were approximately 100 ADR reports of new drugs with SMP per month. As consequence of this ADR reporting via e-mail, UH4 received feedback from Thai FDA that incomplete basic information was age, gender and BW.

*"We could not fill in data on HPVC website within 1 month due to more than 100 ADR cases of new drugs with SMP per months and lack of staff. According to scan QR code, data were recorded in Google sheet. Then, Excel file was forwarded to Thai FDA. We discussed with Thai FDA to allow sending ADR reports via e-mail and Thai FDA agreed. Thai FDA also replied e-mail each month to confirm receiving ADR reports." (UH4-OPD pharmacist)*

*"There was feedback from Thai FDA in March 2021. Thai FDA requested baseline characteristics including age, gender, and BW but we did not re-send this information to Thai FDA. It was difficult to review due to a lot of cases. Previously, Thai FDA did not mention the requirement of age, gender and BW. I was thinking whether we should add these baseline characteristics into Google form. If I added age, gender and BW, I was afraid that Google form was un-user friendly. This*

*would lead to non-compliance in ADR reporting from operational pharmacists." (UH4-OPD pharmacist)*

**Number of ADR reports of new drugs with SMP**

Number of ADR reports of new drugs with SMP were under-reported from drug companies and hospitals. The gap in real practices for hospitals were that there were several items of new drugs with SMP, several number of patients, pharmacists' workload and inadequate staff.

Overall, the compliance of drug companies and hospitals was good in reporting complete ADR information, reporting both serious ADR and non-serious ADR following timetable. However, there was under-reporting of ADR of new drugs with SMP.

**Risk assessment**

The purpose of risk assessment was to evaluate benefit-risk balance of new drugs with SMP in order to take regulatory action and remove new drugs from SMP.



The components of risk assessment included periodic safety update report (PSUR), national database of ADR reports, and decision on risk assessment. PSUR and national database of ADR reports were data sources for risk assessment to take regulatory action and remove new drugs from SMP. Summaries of risk assessment were illustrated in table 30

**Periodic safety update report (PSUR)**

The purpose of PSUR was to support sufficient data to committee to consider benefit-risk balance.

Timetable to submit PSUR

Basically, drug company was responsible for submitting PSUR every 4 months and comprehensive PSUR after completing monitoring period 2 years for new drugs with SMP to Thai FDA. All 6 drug companies (100.00%) asserted that they submitted PSUR following the timetable. One drug company (16.67%) commented that there was no exact month to submit PSUR specified by Thai FDA (DTC1). However, pre-marketing regulatory authorities did not check time to submit PSUR from drug companies.

PSUR review

One drug company (16.67%) needed to know how FDA reviewed PSUR every 4 months. Thai FDA should feedback this information to drug companies (DTC1). Pre-marketing regulatory authority who was the expert stated that the purpose of submitting PSUR every 4 months was to know whether there was under reporting. If there was sign of under-reporting, it needed to check with drug companies and hospitals. However, there was no staff responsible for this task. Therefore, there was no feedback to drug companies and hospitals (Pre-Thai FDA1 expert). Two pre-marketing operational regulatory authorities expressed that PSUR every 4 months was only notification. Only comprehensive PSUR was considered at the time of removing

new drugs from SMP (Pre-Thai FDA2, Pre-Thai FDA3) whereas post-marketing regulatory authorities did not request PSUR for risk assessment.

**National database of ADR reports**

The purpose of signal detection and signal assessment from national database of ADR reports was to support sufficient data to committee to consider benefit-risk balance.

Responsible person

Post-marketing division was responsible for processing signal detection and signal assessment. The first step was signal detection followed by signal assessment. Two regulatory authorities were assigned for detecting signal and 2 regulatory authorities were designated for assessing signal. The signal detection committee and signal assessment committee consisted of representatives from post-marketing division and external experts. Three representatives from post-marketing division were the secretary of signal detection committee and signal assessment committee. The meeting was arranged every 4 months.



Signal detection

Local data source was the national database of ADR reports for signal detection. The data were analyzed every 6 months for all medicinal products. Regulatory authority focused on serious and unknown ADR. However, regulatory authority did not consider whether it was new drug with SMP. Foreign data source was WHO-Vigilize. Regulatory authority accessed on signal topic providing worldwide signals

with statistical significance. It was easy to understand. In addition, literature review was gathered from journal of epidemiology and drug safety.

The criteria for signal detection were that reporting odd ratio (ROR) was more than 1, minimum number of ADR reports was 3 and critical term of ADR following WHO. In addition, it needed causality assessment at possible level, probable level and certainty level to include in signal detection. The output was potential signal sent to signal assessment committee. However, there was no signal of new drugs with SMP due to insufficient ADR reports for signal detection.

The difficult task of signal detection was that it took time to clean and analyze data due to a lot of information. Regulatory authority needed new training in statistic such as proportional IC mentioned in WHO and statistical program such as SQL or program R.

Signal assessment



Regulatory authority mainly focused on serious ADR and unknown ADR. Serious ADR was more important than non-serious ADR. Regulatory authority verified information in the national database of ADR reports case by case. In case of missing information, regulatory authority sent investigation form to reporters. Foreign data sources were obtained from WHO-vigibase. In addition, PIL from US, UK, TGA and Ireland were used as references. However, there was lack of database for literature review, it was difficult to access full papers.

Bradford Hill criteria was used to assess potential signal. Regulatory authority prepared data according to criteria to support the signal committee. Mechanism of action for unknown ADR was the most difficult issue to search. The signals were divided into verified signal, monitored signal and refused signal. Verified signal was defined as signal with strong evidence. Monitored signal was defined as signal with weak evidence. Refused signal was defined as signal without evidence. Verified signal was conveyed to ADR committee. As aforementioned, there was no signal detection of new drugs with SMP. Therefore, there was no signal assessment for new drugs with SMP.

Supporting signal to pre-marketing division

Post-marketing regulatory authorities usually sent ADR reports as well as signal detection to pre-marketing division. Pre-marketing regulatory authorities replied that ADR reports and signal detection from post-marketing division was only notification. Pre-marketing regulatory authorities did not use these data for assessing benefit-risk balance to remove new drugs from SMP. Pre-marketing regulatory authorities mainly employed comprehensive PSUR submitted by drug companies to consider removing new drugs from SMP.



Accessibility of national database of ADR reports

Drug companies mainly received ADR reports from healthcare professionals. However, there was low number of ADR reports of new drugs with SMP from healthcare professionals. Therefore, drug companies must purchase for ADR

reports from national database of ADR reports. Drug companies requested post-marketing division to share this information to drug companies or allow drug companies to access national database of ADR reports. However, post-marketing regulatory authorities allowed drug companies to access only their ADR reports on national database of ADR reports. Drug companies must pay for ADR reports because of private sector.

*"Thai FDA should allow drug company to access national database of ADR reports." (MNC3)*

*"Foreign auditor was surprised why Thai FDA did not report ADR back to drug company and why drug company must pay for ADR reports from Thai FDA. Thai FDA should share this information to drug company." (DTC2)*

*"I was confused about why drug company must pay for ADR reports from national database of ADR reports. Thai FDA should coordinate within organization about supporting ADR report. However, the payment was beneficial for Thai FDA to further develop system." (MNC2)*

*"There was no benefit from buying ADR reports from national database of ADR reports. Regulation did not mention about payment for ADR reports." (MNC1)*

**Decision on benefit-risk assessment for taking regulatory action**

Responsible person

ADR committee had duty to consider benefit-risk balance and

recommend regulatory action taken such as label change, suspension or withdrawal. Finally, national drug committee adjudicated the recommendation from ADR committee to take regulatory action. ADR committee comprised the representatives from pre-marketing division, post-marketing division of Thai FDA and external experts in medicines, pharmacology, pharmacovigilance and pharmacoepidemiology. There was no publication of experts list for taking regulatory action. ADR committee meeting was arranged every 3 months. There was no problem in terms of making appointment.

Decision on risk assessment

ADR committee considered data sources supported from post-marketing regulatory authorities to recommend regulatory action to be taken. Criteria for benefit-risk assessment were applied from WHO. Generally, ADR committee accepted verified signal and recommended to change label. In case of no signal in Thai database whereas the foreign regulatory action taken was label change, the committee might consider label change for Thailand because foreign data sources provided strong evidence. Committee could make decision at the time of meeting. However, there was no signal of new drugs with SMP to consider for taking regulatory action.



**Decision on benefit-risk assessment for removing new drugs from SMP**

Responsible person

Pre-marketing division was mainly responsible for removing new drugs from SMP. There were only 1 or 2 external experts and 1 regulatory authority to judge whether new drugs could be removed from SMP. However, there was no

committee for considering removing new drugs from SMP. The reason for this was that it was cumbersome. Pre-marketing division had limited human resources.

*"If pre-marketing division arranged regular meeting, it would take time, waste time and increase workload." (Pre-Thai FDA2)*

Criteria for removing new drugs from SMP

There were no standard criteria to consider benefit-risk balance to remove new drugs from SMP. It depended on regulatory authorities and external experts' consideration. The problem was that ADR reports of new drugs with SMP were insufficient. Regulatory authorities and experts also consider foreign data sources.

*"Mostly, I considered foreign data sources. Local data source was not strong. It was still under-reporting" (Pre-Thai FDA1 expert).*

*"There were no standard criteria for removing new drugs from SMP. It depended on regulatory authorities and external experts' consideration. There was different judgement of individual regulatory authorities and external experts." (Pre-Thai FDA2)*



Number of ADRs requirement for removing new drugs from SMP

Drug companies commented that Thai FDA did not specify the exact number of ADR reports for removing new drugs from SMP and the definition of enough ADR reports was unclear. From drug companies' experiences, number of ADR reports that new drugs could be removed from SMP was 30-40 cases or 50-100 cases. Pre-marketing regulatory authorities replied that there was no minimum number of

ADR reports requirement. From pre-marketing regulatory authority's experience, the number of ADR reports that new drugs could be removed from SMP was less than 10 cases.

*"There were no criteria for minimum number of ADR reports. Thai FDA addressed only enough case report. Drug companies must judge by themselves." (DTC1)*

*"Although low number of ADR reports (only 50-100 cases or less than 50 cases), it was so curious why new drugs could be removed from SMP." (MNC1)*

*"In case of anti-cancer, number of ADR reports that new drugs could be removed from SMP were 30-40 cases." (MNC2)*

*"I requested drug companies to collect more data, if there was no ADR with using volume only 50-100 doses within 2 years. The acceptable using volume were 1,000 or 10,000 up. However, there was no minimum number of ADR reports requirement. In real practice, the number of ADR reports that new drugs could be removed from SMP were less than 10 cases." (Pre-Thai FDA2).*

*"There was no minimum ADR reports requirement. If there were small number of ADR reports, I requested drug companies to search more data such as literature review." (Pre-Thai FDA3)*

Actual monitoring period of new drugs with SMP

From Pre-Thai FDA2's experience, most biologic products could be removed from SMP within 2 years. However, some products needed to extend monitoring period due to small number of ADR reports. From Pre-Thai FDA3's experience, all biologic products could be removed from SMP within 2 years because there were known ADRs and there was no new ADR or serious ADR.

According to drug companies' experience, some new drugs could be removed from SMP within 2 years while some new drugs could not be removed within 2 years due to insufficient data. If drug companies considered that there was low number of ADR reports. Drug companies must request to extend monitoring period.

Consensus

If external experts and regulatory authorities had different decision, the main decision was Thai FDA. Opinion from external expert was comment.



Time to make decision

Pre-marketing division specified time for expert within 2 months to consider new drugs removed from SMP. Pre-Thai FDA2 mentioned that defined time for considering was 2 months for experts. However, external experts spent time more than 2 months due to a lot of routine workloads whereas Pre-Thai FDA3 stated that experts could make decision within pre-defined time.

The process of removing new drugs from SMP was separated from the process of taking regulatory action. Pre-marketing division was responsible for removing new drugs from SMP whereas post-marketing division did not pertain in this process. The weakness of local data source was insufficient ADR reports of new drugs with SMP to underpin signal detection and removing new drugs from SMP.

**Risk communication**

The purpose of risk communication was to inform new ADRs to targeted healthcare professionals. Risk communication channels and timetable to communicate were described for Thai FDA bulletin and DHPC of drug companies. The principle of risk communication for new drugs with SMP and non-SMP drugs was similar. Summaries of risk communication were presented in table 31.

**Thai FDA bulletin**

Risk communication channels and time to communicate



Previously, hard copy was available. Currently, post-marketing division communicated risks via electronic channels including e-mail, Line, website and Facebook. The targeted audiences were healthcare professionals in the hospitals. At present, there were approximately 700-800 members receiving news via e-mail. The lists of members were updated every 2 years. Timetable to communicate risks was within 2 weeks after committee made decision. Bulletins were published every 3 months while HPVC safety news was distributed depending on issues. From regulatory authorities' perspective, it could not confirm that healthcare professionals received

risk communication via hard copy, website and Facebook. On the other hand, it ensured that healthcare professionals who were the members received information via e-mail and Line reached some healthcare professionals.

A total of 16 pharmacists, 11 pharmacists (68.75%) received Thai FDA bulletin but there was no issue about SMP. Five DIS-pharmacists (45.45%) directly received bulletin from Thai FDA via post whereas 6 pharmacists (54.54%) received information via hospital pharmacy Line group. Of these 11 pharmacists, 9 pharmacists occasionally received, 1 pharmacist regularly received and 1 pharmacist rarely received Thai FDA bulletin. On the other hand, 5 pharmacists (31.25%) never received bulletin from Thai FDA. In addition, 4 pharmacists (25.00%) also occasionally accessed HPVC website if they were available whereas twelve pharmacists (75.00%) never accessed HPVC website. All pharmacists never received risk communication via e-mail, Line and Facebook. All physicians (100.00%) never received Thai FDA bulletin. Healthcare professionals suggested that electronic transmission including e-mail and Line was the favorable channel because it could be kept in PDF file and it was easy to access anytime.



**DHPC of drug company**

The purpose of sending DHPC was to inform healthcare professionals regarding new ADRs while waiting for update PIL prepared by drug companies. DHPC for new drugs with SMP and non-SMP drugs was similar. DHPC format was adopted from global template. Therefore, this confirmed that contents of DHPC were complete.

DHPC communication channels and time to communicate

All 6 drug companies (100.00%) mentioned that medical representatives provided DHPC to healthcare professionals while one drug company (16.67%) also sent via post (MNC1). Drug companies distributed new ADR within 1-3 months. Six physicians (75.00%) never received DHPC. Only 2 physicians (25.00%) received DHPC about new ADR of anti-cancer via e-mail and letter.

*"I received DHPC from drug companies regarding anti-cancer induced infusion reaction. It was new ADR with high frequency. I received both e-mail and letter from drug companies. I prefer e-mail. The advantage was that it was easy to access and could re-check." (UH4-Oncologist)*

Three DIS pharmacists (18.75%) occasionally received letter from drug companies but there was no issue about SMP. UH1-DIS pharmacist received letter from drug company regarding update PIL of non-SMP. UH3-DIS pharmacist received DHPC from drug company informing new ADR of non-SMP. TH3-DIS pharmacist received letter from drug companies about problem of ingredient of non-SMP. On the other hand, 13 pharmacists (81.25%) never received letters from drug companies.



It indicated that risk communication distributed by Thai FDA and drug companies did not reach all healthcare professionals. It did not accomplish the purpose of risk communication.

All abbreviations were mentioned in Appendix S.

Table 24 Risk management plan

| Structures | Thai FDA | | Drug companies | Hospitals |
|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | |
| **RMP guideline** | | | | |
| **: Awareness of RMP guideline** | : All three regulators (100.00%) reached RMP guideline<br>: One regulator (25.00%) informed RMP guideline to drug companies (Pre-Thai FDA1-expert)<br>: Two regulators (75.00%) received internal RMP training. (Pre-Thai FDA2, Pre-Thai FDA3) | : All three regulators (100.00%) reached RMP guideline.<br>: One regulator (25.00%) received internal RMP training (Post-Thai FDA1-Director)<br>: Two regulators (75.00%) received notification document of RMP guideline. (Post-Thai FDA2, Post-Thai FDA3) | : All six drug companies (100.00%) received RMP guideline from PREMA. | : NA |
| **: Understanding of RMP guideline** | | | | |
| : Clarity of RMP guideline | : Clear | : Clear | : Clear | :NA |
| : RMP product coverage | : Two regulators (75.00%) agreed. (Pre-Thai FDA1 expert, Pre-Thai FDA3)<br>: One regulator (25.00%) disagreed (Pre-Thai FDA2) | : Two regulators (75.00%) agreed. (Post-Thai FDA2, Post-Thai FDA3)<br>: One regulator (25.00%) disagreed. (Post-Thai FDA1-Director) | : Two drug companies (33.33%) agreed. (MNC3, DTC2)<br>: Two drug companies (33.33%) disagreed. (MNC4, DTC1)<br>: Two drug companies (33.33%) did not concern. (MNC1, MNC2) | :NA |

| Structures | Thai FDA | | Drug companies | Hospitals |
|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | |
| **Processes** | | | | |
| **: RMP submission** | | | . | |
| : RMP review | : Safety specification was complete.<br>: Risk minimization activities and pharmacovigilance activities were appropriate. | :NA | : RMP review was no problem. | :NA |
| : Global and local RMP | : All drug companies submitted global RMP.<br>: Not all drug companies submitted local RMP. | :NA | : All six drug companies (100.00%) submitted both global and local RMP | :NA |
| **: RMP update** | : There was no new safety concern to update RMP. (Pre-Thai FDA2)<br>: There was new safety concern to update RMP. (Pre-Thai FDA3) | :NA | : All six drug companies (100.00%) had no experience in RMP update due to no new safety. | :NA |
| **: Inspection** | : No inspection. | : No inspection. | : NA | :NA |

**Table 25 Safety monitoring program (SMP) structures: SMP guideline, SMP protocol and national database of approved drugs**

| Structures | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **SMP guideline** | | | | | |
| **: Awareness of SMP guideline** | : All three regulators (100.00%) received SMP guideline.<br>: Two regulators (75.00%) received notification of SMP guideline (Pre-Thai FDA2, Pre-Thai FDA3)<br>: One regulator (25.00%) informed SMP guideline to drug companies (Pre-Thai FDA1-expert). | : All three regulators (100.00%) received notification of SMP guideline.<br>: Arranged regular meeting with hospitals 2 times/year but there was no issue related to SMP. | : All six drug companies (100.00%) received SMP guideline from PREMA. | : Twelve pharmacists (75.00%) never received SMP guideline.<br>: Two pharmacists (12.50%) accessed SMP guideline from Thai FDA website.<br>: Two pharmacists (12.50%) attended conference. | : All physicians (100.00%) never received SMP guideline. |

| Structures | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **: Understanding of SMP guideline** | | | | | |
| : Clarity of SMP guideline | : Methods of reminding should depend on risk of medicinal products. (Pre-Thai FDA1 expert) | : No PV inspection issues in SMP guideline. (Post-Thai FDA1-Director) | : Four drug companies (66.67%) commented that pre-launching definition was obscure. (MNC2, MNC3, MNC4, DTC2)<br>: Two drug companies (33.33%) mentioned that methods of early informing and reminding were vague. (DTC1, DTC2)<br>: Two drug companies (33.33%) stated that methods of monitoring new drugs with SMP-risk level 1 was in general. (MNC1, MNC3) | : NA | : NA |

| Structures | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| : Risk-based approach<br>: Method of monitoring<br>: Monitoring period | : All three regulators (100.00%) agreed with SMP risk-based approach | : All three regulators (100.00%) agreed with SMP risk-based approach | : All six drug companies (100.00%) agreed with risk-based approach. | : One pharmacist agreed with risk-based approach. (UH1-ADR pharmacist) | : NA |
| **SMP protocol** | : Regulators confirmed that SMP protocols submitted by drug companies were suitable for each risk level. (Pre-Thai FDA1 expert) | : NA | : Five drug companies (83.33%) had SMP protocol for risk level 2 using intensified reporting.<br>: One drug company (16.67) had SMP protocol for risk level 1 using registry. (MNC1) | : Hospitals developed their own SMP protocol due to HA enforcement.<br>: Five hospitals (62.50%) had SMP protocol for pharmacists.<br>: Three hospitals (37.50%) had no SMP protocol for pharmacists. | : No SMP protocol for physicians. |

| Structures | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **National database of approved drugs**<br>: Accessibility<br>: Convenient | : Responsible for updating status of new drugs with SMP. | : Regulators could not access internal database to check status of new drugs with SMP. | : Drug companies knew their product status. | : Three hospitals (37.50%) enabled to access database and it was convenient.<br>: Three hospitals (37.50%) unenabled to access database and it was inconvenient.<br>: Two hospitals (25.00%) were unable to access database. | : NA |
| **The existing lists of new drugs with SMP.** | : There were no existing lists of new drugs with SMP for each risk level at Thai FDA. | : There were no existing lists of new drugs with SMP for each risk level at Thai FDA. | : Five drug companies (83.33%) had new drugs with SMP risk level 2.<br>: One drug company (16.67%) had new drug with SMP risk level 1 and risk level 2. (MNC1) | : Six hospitals (75.00%) had lists of new drugs with SMP.<br>: Two hospitals (25.00%) had no list of new drugs with SMP. (UH1, TH2)<br>: However, hospitals did not categorize by risk level. | : NA |

| Structures | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **Dissemination of lists of new drugs with SMP within the hospitals** | : NA | : NA | : NA | : Five hospitals (62.50%) disseminated lists of new drugs with SMP.<br>: Channels of dissemination were hospital intranet (UH2, UH4), hospital website (UH3, UH5) and Line group (TH1)<br>: All pharmacists in these hospitals confirmed that they reached this information.<br>: Three hospitals (37.50%) did not distribute lists of new drugs with SMP. | : Physicians did not know channels to access lists of new drugs with SMP. |

Table 26 Distribution of safety information of new drugs with SMP

| Processes | Thai FDA | | Drug companies | Hospital | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **: Timetable of early informing and reminding** | : No inspection<br>: Regulators confirmed that they received the reports of the implementation of activities. | : No inspection<br>: Regulators confirmed that they received the reports of the implementation of activities. | : All drug companies (100.00%) asserted that they provided early informing and reminding. | : NA | : All physicians (100.00%) confirmed that they received information before launching and after launching. |
| **: Methods of early informing and reminding** | : It depended on risk of products. If it was high risk, it needed training. | : It depended on drug companies' opinion. | : All drug companies mainly early informed and reminded physicians by medical representatives.<br>: MNC2 and MNC4 also used additional methods by sending letter via post and e-mail, respectively. | : NA | : Physicians confirmed that they received early informing and reminding by medical representatives.<br>: Physicians did not receive post letter or e-mail. |

| Processes | Thai FDA | | Drug companies | Hospital | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **: Awareness of important ADR** | : No data source of ADR information at Thai FDA. | : Lack of PIL to support signal detection and signal assessment.<br>: Focused on serious ADR and unknown ADR. | : Drug companies provided PIL, educational materials to hospital pharmacists and hospital physicians. | : Pharmacists received safety information as PIL and drug monograph.<br>: Pharmacists commented that drug companies provided whole information. They must extract significant ADR information from PIL. | : Physicians confirmed that they received guidance on prescribing from drug companies.<br>: Physicians stated that drug companies provided all information focusing on efficacy. |
| **: Usability of safety information** | : NA | : NA | : NA | : Six hospitals (75.00%) had check lists for ADRs of new drugs with SMP.<br>: Two hospitals (25.00%) had no check list for ADRs of new drugs with SMP. | : There was no checklist for ADR of new drugs with SMP for physicians. |

Table 27 Methods of monitoring new drugs with SMP: Drug companies

| Processes | Thai FDA<br>Pre-marketing division | Thai FDA<br>Post-marketing division | Drug companies | Hospital physicians |
|---|---|---|---|---|
| **Route of reporting from physicians to drug companies.** | : NA | : NA | : All drug companies mentioned that physicians could report ADR to drug companies via medical representatives and call center. | : Physicians mentioned that they mainly informed ADR to medical representatives by verbal.<br>: Physicians did not know other routes of ADR reporting to drug companies. |
| **Route of reporting from medical representatives to contact person for PV at drug companies** | : NA | : NA | : Two drug companies (33.33%) used paper form (MNC4, DTC1)<br>: Two drug companies (33.33%) used e-mail and telephone (MNC1, DTC2)<br>: Two drug companies (33.33%) used drug companies' application (MNC2, MNC3) | : NA |
| **Methods of monitoring new drugs with SMP risk level 1** | : No PV inspection | : No PV inspection | : One drug company (16.67%) monitored new drugs with risk level 1 using manual registry | : NA |

Table 28 Methods of monitoring new drugs with SMP: Hospitals

| Processes | Physicians | Pharmacists-passive method | Pharmacist-ambulatory | Pharmacist-Additional method (SMP protocol) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | (UH1, TH2) | TH3 | UH2 | UH3 | UH4 | UH5 | TH1 |
| **Targeted new drugs with SMP subject to monitor** | Not specified | Not specified | Not specified | All 74 items | Select 60 items from 100 items | Select 18 items from 100 items | Select 2 items from 100 items | All 4 items |
| **Risk minimization activities** | Regular | Regular | Advised common ADR to patients. | Regular | Regular | Advised common ADR to patients. | Regular | Regular |
| **Pharmacovigilance activities** | | | | | | | | |
| : Identifying methods | Regular | Regular | Regular | Paper-note | Hospital website check list for ADR | Scan QR code check list for ADR | Telephone to patients and review OPD card | Telephone to physicians |
| : Timetable to follow-up | Routine follow-up | Not specified | Routine follow-up | Could not follow-up every visit | Could not follow-up every visit | Could follow-up every visit | Could follow-up every visit | Every 6 months |
| : Causality assessment | Regular | Regular | Regular | Regular | Regular | No causality assessment | Regular | Regular |

| **Processes** | **Physicians** | **Pharmacists-passive method** | **Pharmacist-ambulatory** | **Pharmacist-Additional method (SMP protocol)** | | | | |
|---|---|---|---|---|---|---|---|---|
| | | (UH1, TH2) | TH3 | UH2 | UH3 | UH4 | UH5 | TH1 |
| : Type of ADR report | Type B (drug allergy) and serious Type A (side effect) | All ADR types | Type B (drug allergy) and serious Type A (side effect) | All ADR types | All ADR types | All ADR types | All ADR types | All ADR types |
| : Number of ADR reports | : Not specified | : Not specified | : Low | : Low | : 50 cases previous year | : 100 cases/month | : 23 cases previous 6 months | : Low |

Table 29 ADR reporting from drug companies and hospitals to Thai FDA

| Processes | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| : ADR form | : NA | : No SMP identification | : No SMP identification | : No SMP identification | : No SMP identification |
| : Completeness of ADR information | : NA | : Regulators confirmed that ADR reports were mostly complete (score 0 and 1). | : Five drug companies (83.33%) could complete ADR before sending to Thai FDA.<br>: One drug company (16.67%) commented that ADR reports were complete 50% due to lack of age, gender. (MNC1) | : All eight hospitals (100.00%) could complete all basic information before sending to Thai FDA. | : NA |
| : Types of ADR report | : NA | : Regulators confirmed receiving both serious ADR and non-serious ADR. | : All six drug companies (100.00%) reported all types of ADR. | : Seven hospitals (87.50%) reported all types of ADR.<br>: One hospital (12.50%) reported type B and serious type A, but did not report non-serious type A. (TH3) | : NA |

| Processes | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **: Time to report ADR** | : NA | : Regulator confirmed that drug companies reported fatal cases within 24 hours. (Post-Thai FDA1 director) | : All six drug companies (100.00%) reported ADR following timetable. | : Seven hospitals (87.50%) reported ADR within 1 month.<br>: One hospital (12.50%) reported every 3 months. (UH3) | : NA |
| **: Routes of reporting** | | | | | |
| : Website | : NA | : Regulators prefer website. | : All six drug companies (100.00%) reported ADR via website. | : Five hospitals (62.50%) reported ADRs via website | : NA |
| : Post | : NA | : NA | : NA | : Two hospitals (25.00%) reported via post (UH3 and UH5). | : NA |
| : E-mail | : NA | : NA | : NA | : One hospital (12.50%) reported via e-mail (UH4). | : NA |
| **Number of ADR report of new drugs with SMP** | : NA | : Could not identify which ADR reports belonged to SMP. | : Low number of ADR reports of new drugs with SMP. | : Low number of ADRs of new drugs with SMP due to several items, several patients, workload and insufficient staff. | : NA |

Table 30 Risk assessment

| Processes | Thai FDA | | Drug companies | Hospitals |
|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | |
| **PSUR** | : PSUR every 4 months was only notification. Regulators considered comprehensive PSUR.<br>: Regulators did not check time to submit PSUR. | : Did not request PSUR. | : All six drug companies (100.00%) confirmed that they submit PSUR every 4 months.<br>: One drug company (DTC1) commented that there was no pre-specified month to submit PSUR. | : NA |
| **National database of ADR reports** | : Signal detection and ADR report from post-marketing was only notification. | : ADR reports of new drugs with SMP were insufficient for signal detection. | : All drug companies (100.00%) requested to access national database of ADR reports. | : NA |
| **Decision on risk assessment** | | | | |
| : Advisory committee | : Pre-marketing regulators were responsible for removing new drugs from SMP.<br>: There was no committee to remove new drugs from SMP | : ADR committee was responsible for recommending regulatory action taken.<br>: National advisory committee was responsible for making decision on regulatory action taken. | : NA | : NA |

| Processes | Thai FDA | | Drug companies | Hospitals |
|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | |
| : Decision on risk assessment | : There were no standard criteria.<br>: It was individual regulators and experts' opinion.<br>: Regulators commented that local data source was not strong.<br>: Most biologic products were removed within 2 years (Pre-Thai FDA2).<br>: All biologic products were removed within 2 years (Pre-Thai FDA3). | : Benefit-risk assessment framework<br>: There was no signal of new drugs with SMP for taking regulatory action. | : If drug companies felt that there was inadequate safety data, drug companies might delay in removal. | : NA |

**Table 31 Risk communication**

| Processes | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **Bulletin from Thai FDA** | | | | | |
| : Risk communication channels for bulletin | | | | | |
| : Hard copy | : NA | : Could not ensure it reached all HCPs. | : NA | : Five DIS pharmacists (45.45%) received via post. | : No |
| : E-mail | : NA | : It reached HCPs who were the members. | : NA | : No | : No |
| : Line | : NA | : It reached some HCPs. | : NA | : Four pharmacists (25.00%) accessed website | : No |
| : Website | : NA | : Could not ensure it reached all HCPs. | : NA | : No | : No |
| : Facebook | : NA | : Could not ensure it reached all HCPs. | : NA | : No | : No |

| Processes | Thai FDA | | Drug companies | Hospitals | |
|---|---|---|---|---|---|
| | Pre-marketing | Post-marketing | | Pharmacists | Physicians |
| **DHPC from drug companies** | | | | | |
| : Risk communication channels for DHPC | :- | :- | : All six drug companies (100.00%) communicate by medical representatives.<br>: One drug company (16.67%) also sent DHPC via post.<br>(MNC1) | : Three DIS pharmacists (18.75%) received letters from drug companies about updated PIL but there was no issue about SMP.<br>: Thirteen pharmacists (81.25%) never received letters from drug companies. | : Two physicians (25.00%) received DHPC.<br>: Six physicians (75.00%) never received DHPC. |

# CHAPTER V

# DISCUSSION

## Discussion of the first objective: Review pharmacovigilance system of new drugs in targeted countries

Guideline was the important structure facilitating function of the pharmacovigilance system of new drugs. Most of countries mentioned the requirement of post-authorization safety studies within pre-specified monitoring period in guideline and mostly operated in high income countries. Thailand also had a particular guideline for new drugs, namely safety monitoring program (SMP). Although Thailand possessed authorized drug product database to check status of new drugs with SMP, there was no drug information available in the authorized drug product database. Public accessibility of ADR report was not available in Thailand.

RMP has been required for all types of new drugs in most countries. Thailand requested RMP for only biologic products and biosimilars that was narrower scope than those in other countries. The suggestion for countries without RMP requirement was that regulatory authorities might request RMP depending on risk-based approach as well as accept the EU-RMP or US-REMS templates.

Only Thailand required drug companies to conduct active vigilance of new drugs approved with clinical trial phase 2 for all cases every visit whereas other types of new drugs were monitored using intensified reporting system. This indicated that

types of new drugs required for active vigilance in Thailand was narrower than other countries that required drug companies to perform post-authorization safety studies for all types of new drugs.

Most countries had fixed pre-specified monitoring period of 5 years. Pre-specified monitoring period in China, Japan, Korea and Thailand depended on types of new drugs. Thailand had the least pre-specified monitoring period with 1-2 years which compared to China (3-5 years), Korea (4-6 years) and Japan (4-8 years). New chemical entity seemed to be monitored for longer period than other types. The reason for this was that there was limited safety data of new chemical entities compared with other types of new drugs.

Website was the most favorable ADR reporting channel because it was convenient. In addition, the information was automatically entered to database. Thailand also mainly reported ADR via website. For post, phone, fax, e-mail, the information was manually recorded by authority. This might increase workload.



Time to report fatal and serious ADR was more rapid than non-serious ADR in order to speed up regulatory action taken. Thailand required to report serious ADR within 15 days that was similar to most countries. Time to report non-serious ADR was 90 days in most countries whereas Thailand requested to submit non-serious ADR within 60 days. Some countries did not define time to report non-serious ADR. The explanation for this was that those countries did not request to submit non-serious ADR or could submit anytime.

Thailand processed risk assessment to remove new drugs from condition but the publication of risk assessment report and the publication of committee lists was not available on website. Publication of risk assessment reports and publication of committee lists were low proportions in most countries. It indicated that this information might be confidential.

The limitation of searching step was that there was no drug regulatory authority website in 10 countries. The limitation of extracting step was that 4 drug regulatory authority websites were non-English and 38 drug regulatory authority websites did not provide information on pharmacovigilance system of new drugs. It could not conclude that these countries had no pharmacovigilance system of new drugs. In addition, the information was not validated by the regulatory authority in each country. Therefore, the results were mentioned that it could not specify.

**Discussion of the second objective: Assessment of pharmacovigilance system of new drugs in Thailand**



The link between the first objective and the second objective was that pharmacovigilance system of new drugs in Thailand was achieved by several indicators following IPAT and WHO indicators. However, some issues were needed to improve. First, there was the absence of PV inspection. Second, there was no signal detection of new drugs with SMP. Third, the coordination between pre-marketing division and post-marketing division in Thai FDA was not well established. Fourth, the capability of

Thai FDA in RMP review and SMP reports review was unsatisfactory. Fifth, there was no communication to endorse RMP from Thai FDA to hospitals. Sixth, there was no existing lists of new drugs with SMP for each risk level. PV inspection was the complementary outcome indicator of IPAT. Signal identified and regulatory action were the core outcome indicators of WHO. However, IPAT and WHO indicator did not include the third to the sixth issues as the indicators.

At pre-marketing phase, Thai FDA required RMP for biologic products and biosimilars with narrow scope than other countries that RMP was required for all types of new drugs. The reason for this was that biologic products had higher risk than chemical products. Thai FDA also requested drug companies to submit both global RMP and local RMP. The compliance of drug companies was good in global RMP submission whereas the compliance of drug companies was partially good in local RMP submission due to no enforcement or lack of experience in preparing local RMP. Regulatory authorities should assist drug companies in the formulation of the local RMP by selecting the best local RMP and providing to other drug companies to emulate the format. Only pre-marketing regulatory authorities were mainly responsible for RMP submission. It would be better if post-marketing regulatory authorities also participated in this process in order to link RMP between pre-marketing division and post-marketing division.



The SMP structures were available including SMP guideline, SMP protocol and national database of approved drugs. SMP guideline consisted of core components,

but it lacked PV inspection issue. Therefore, regulatory authorities should consider establishing policy for PV inspection.

SMP guideline was translated into SMP protocol prepared by drug companies. However, there was no collaboration of SMP protocol between contact person for PV of drug companies and focal point of hospitals. Therefore, it needed to reinforce the cooperation regarding SMP protocol.

National database of approved drugs was difficult to access and it was inconvenient. The existing lists of new drugs with SMP for each risk level and drug information were not available on national database of approved drugs. Relevant stakeholders needed the updated line listing of new drugs with SMP. Comparison to EMA lists of new medicinal products under additional monitoring, EMA published the update line listing of the status of medicinal products including new entry and removal every 1 month. Thai FDA might adopt this pattern to facilitate hospitals. The contents in database for new drugs with SMP should include PIL, SPC and approved RMP.



Drug companies distributed safety information including PIL and educational materials for healthcare professionals. However, the effectiveness of the educational material was not assessed. In comparison to EU, there was a requirement for conducting studies to evaluate the effectiveness of educational materials. According to systematic review from 23 studies, additional risk minimization activities reached healthcare professionals (69.6%). In addition, EU healthcare professional's knowledge about safety concerns was generally good (>60.0%) (64).

Although Thai FDA summarized annual reports of ADR reports of Thai population in PDF file on HPVC website, healthcare professionals did not reach these data. On the other hand, 7 countries including Australia, Canada, the Netherlands, New Zealand, Singapore, the United Kingdom and the United States provided public accessibility of searchable database of ADR reports allowing healthcare professionals, patients and drug companies to access ADR reports with basically limited information. Thai FDA might develop the searchable national database of ADR reports to support ADR information of Thai population for healthcare professionals.

Under-reporting of ADR reports of new drugs with SMP reflected that the methods of monitoring new drugs with SMP in drug companies and hospitals were ineffective. Drug companies carried out early informing and reminding as well as implementing SMP protocol following risk level. Although drug companies confirmed that they operated these activities, Thai FDA could not ensure whether drug companies conformed with the regulation in real practice due to lack of PV inspection. As a consequence of this, there was low number of ADR reports of new drugs with SMP from drug companies which compared to Japan EPPV. The studies related to Japan EPPV revealed that the number of ADR reports of new drugs increased after implementing these activities(60-62). Furthermore, the developed countries including Canada, Japan and the United States conduct active surveillance to strengthen post-marketing surveillance on behalf of drug regulatory agencies; Canadian Network for observational Drug Effect Studies (CNODES) in Canada, the MIHARI project in Japan and

sentinel initiative in the United States. These developed countries provided budget for pharmacovigilance activities. On the other hand, Thai FDA had no research unit for performing post-authorization safety studies.

At hospital level, most healthcare professionals did not reach SMP guideline. Therefore, the SMP protocol established by hospitals reflected that they did not understand the concept of SMP risk-based approach. The method of monitoring new drugs with SMP was similar for high risk level and low risk level. Hospitals did not consider risk level. Five hospitals had SMP protocol. Of these, 2 hospitals could follow-up all patients and every visit due to selection of small items of new drugs with SMP to monitor and obtained high number ADR reports of new drugs with SMP. Two hospitals could not follow-up all patients and every visit due to monitor several items of new drugs with SMP and several patients receiving new drugs with SMP. Thus, they gathered low number of ADR reports of new drugs with SMP. One hospital could monitor all patients due to a small number of new drugs with SMP and collected a low number of ADR reports of new drugs with SMP. On the other hand, 3 hospitals had no SMP protocol. These 3 hospitals monitored all medicinal products using regular methods. They collected low number of ADR reports of new drugs with SMP. The findings showed that methods of monitoring new drugs with SMP were various among hospitals. Overall, there was low number of ADR reports of new drugs with SMP in most hospitals.

The influencing factor contributing to maximize number of ADR reports of new drugs with SMP in the hospitals was item of new drugs with SMP subject to monitor. However, the criteria for selecting items of new drugs with SMP aimed to monitor did not rely on risk level. Some hospitals chose some items of new drugs with SMP to monitor based on usage volume and interesting ADR whereas some hospitals monitored all items of new drugs with SMP. This indicated that the hospital pharmacists had misconceptions of SMP risk level. Indeed, the principle of SMP risk-based approach required only new drugs with risk level 1 to conduct active vigilance. The suggestion criteria for selecting new drugs with SMP to monitor should be considered according to new drugs with SMP risk level 1 as the first priority to carry out active vigilance. Although hospital SMP protocols were not in line with SMP guideline risk-based approach, the present study revealed that hospitals made an effort to monitor new drugs with SMP by using active surveillance which compared to a previous study that hospitals monitored new drugs with SMP using passive surveillance (18).



The compliance of drug companies and hospitals was good in reporting complete ADR reports and reporting all types of ADR following the timetable. Hospital pharmacists were the main persons to report ADRs of new drugs with SMP. All hospital pharmacists knew that new drugs with SMP should be reported for all types of ADR. On the other hand, all hospital physicians did not know to report all types of ADR of new drugs with SMP. Physicians informed only serious ADRs more than non-serious

ADRs to pharmacists. This was consistent with studies in the UK and Ireland (50, 51). For the UK studies, most oncology pharmacists (87%) knew that new medicines with inverted black triangle should be reported all ADRs whereas 38% of oncologists were aware of this issue. Most oncologists (71%) thought that the behavior on ADR reporting did not alter whether the medicine had presence or absence of inverted black triangle. For Ireland, 86.4% of pharmacists had higher awareness of inverted black triangle which compared to 35.6% of general practitioners.

Thai FDA had no timetable to submit PSUR whereas EMA specified reference date lists for PSUR submission. Thai FDA post-marketing division did not use PSUR submitted by drug companies to evaluate benefit-risk balance. Thai FDA post-marketing division prepared data by themselves while EMA-Pharmacovigilance risk assessment committee (PRAC) employed PSUR to consider benefit-risk balance to take regulatory action. Therefore, Thai FDA post-marketing division might also consider PSUR submitted by drug companies and address the defined time for PSUR submission.



Thai FDA separately operated risk assessment for taking regulatory action from removing new drugs from SMP. Thai FDA pre-marketing division functioned for removing new drugs from SMP by 1 or 2 experts and 1 regulatory authority while Thai FDA post-marketing division had duty for taking regulatory action by ADR committee and national advisory committee. Indeed, it needed to merge 2 processes including take regulatory action and remove new drugs from SMP in 1 committee as EMA that

PRAC was responsible for assessing benefit-risk balance for both taking regulatory action and removing new drugs from condition.

Thai FDA did not publish lists of committee members and risk assessment report. As the results from the first objective, 20 countries published lists of committee member and 8 countries issued risk assessment reports on their regulatory authority websites in order to reveal transparency of the processes of making decision by the committee. Thai FDA might ponder this aspect.

Risk communication did not reach all healthcare professionals. Healthcare professionals in Thailand prefer electronic channels rather than hard copy as well as most EU general practitioners (40). There was no issue about SMP in Thailand bulletin whereas Japan published the update lists of new drugs subject to EPPV in newsletter every month. Thailand might consider addressing new drugs with SMP subject to monitor in bulletin.



Policy recommendation

Thai FDA should establish policy for pharmacovigilance inspection. New drugs with risk level 1 might be priority. Thai FDA required only new drugs approved with clinical trial phase 2 to conduct active vigilance which compared to other countries that all types of new drugs were mandated to perform active studies. Thai FDA might also consider extending to cover new chemical entities because this type of new drug had less safety data than other types of new drugs in order to strengthen post-marketing surveillance.

# CHAPTER VI

# CONCLUSION

**Conclusion of the first objective: Review pharmacovigilance system of new drugs in targeted countries**

The important components for pharmacovigilance system of new drugs were that new drugs with condition required to conduct post-authorization safety studies within pre-specified monitoring period and process risk assessment to remove new drugs from condition in 30 countries (34.48%). Of these, 28 countries were high income countries and 2 countries were upper-middle income countries (Bulgaria and Thailand). Therefore, the performance of pharmacovigilance system of new drugs in Thailand was equal to high income countries. Overall, the existing components of pharmacovigilance system of new drugs in Thailand included pharmacovigilance system guideline, authorized drug product database, risk management plan requirement, post-authorization safety studies within pre-specified monitoring period, ADR reporting channels, time to report ADR, PSUR submission interval, risk assessment to remove new drugs from condition and take regulatory action, and risk communication. However, the absent component was pharmacovigilance inspection in Thailand.

**Conclusion of the second objective: Assessment of pharmacovigilance system of new drugs in Thailand**

The achievable issues of risk management plan (RMP) included that the compliance of drug companies was good in RMP submission with addressing complete safety specification, appropriate risk minimization activities and appropriate pharmacovigilance activities. However, the unachievable issue of risk management plan was that there was no inspection.

The achievable issues of safety monitoring program (SMP) included that the compliance of drug companies and hospitals was good in reporting complete ADR information and reporting all types of ADRs following the timetable. However, the unachievable issues of SMP were that SMP guideline did not reach healthcare professionals in the hospitals. The existing lists of new drugs with SMP for each risk level and PIL were not available on national database of approved drugs. Local data source for signal detection and removing new drugs from SMP was insufficient. Risk communication did not reach all healthcare professionals.



According to structures, Thai FDA coordinated with drug companies in establishing RMP and SMP guideline. However, Thai FDA did not include hospitals as targeted audiences. Therefore, Thai FDA and drug companies understood the guideline whereas hospitals did not understand the guideline. For processes, although drug companies complied with activities following guideline, Thai FDA could not confirm whether drug companies implemented the activities in real practice due to lack of PV

inspection. Thai FDA regularly monitored ADR for all types of drugs. The importance of the differentiation of new drugs from non-new drugs was less emphasize. For the output, the number of ADR reports of new drugs with SMP was low proportion. It was insufficient to detect signal and to support to remove new drug from SMP.

# Appendices

## Appendix A -Questionnaire

**Semi-structure questionnaire guide for Thai FDA, drug companies and hospitals**

**Key informants were interviewed to express their opinion following these topics.**

| Components | Thai FDA | Drug companies | Hospitals |
|---|---|---|---|
| **RMP structures** | | | |
| **: RMP guideline**<br>: Awareness<br>: Understanding (clarity and RMP products coverage) | / | / | - |
| | | | |
| **RMP processes** | | | |
| **: RMP submission** | / | / | - |
| **: RMP update** | / | / | - |
| **: Inspection** | / | / | - |
| | | | |
| **SMP structures** | | | |
| **: SMP guideline**<br>: Awareness<br>: Understanding (clarity and opinion on SMP risk-based approach) | / | / | / |
| **: SMP protocol** | / | / | / |
| **: National database of approved drugs**<br>: Accessibility<br>: Convenience | / | / | / |
| **: The existing lists of new drugs with SMP**<br>: Dissemination | / | / | / |
| | | | |
| **SMP processes** | | | |
| **: Methods of monitoring** | | | |
| : Risk minimization activities<br>: Compliance of pre-prescribing and routine follow-up<br>: Compliance of ADR management<br>: Compliance of counselling | - | - | / |

| Components | Thai FDA | Drug companies | Hospitals |
|---|---|---|---|
| : Pharmacovigilance activities<br>: Identifying method and data record<br>: Timetable to follow-up<br>: Causality assessment | - | - | / |
| **: ADR reporting to Thai FDA** | | | |
| **: Completeness of ADR information** | / | / | / |
| **: Type of ADR report** | / | / | / |
| **: Time to report ADR** | / | / | / |
| **: Route of ADR reporting** | / | / | / |
| **: Number of ADR reports** | | | |
| **: Risk assessment** | | | |
| **: PSUR**<br>: Timetable to submit PSUR<br>: PSUR review | / | / | - |
| **: National database of ADR reports**<br>: Signal detection and signal assessment | / | / | - |
| **: Committee**<br>: Qualification<br>: Quantity<br>: Frequency of meeting<br>: Time to make decision | / | / | - |
| **: Decision on risk assessment** | / | / | - |
| **: Risk communication** | | | |
| **: Newsletter from Thai FDA**<br>: Risk communication channels<br>: Timetable to communicate | / | - | / |
| **: DHPC from drug companies**<br>: Risk communication channels<br>: Timetable to communicate | - | / | / |

# Appendix B -Articles from systematic review

| No. | Countries | Level of income | No. | Articles |
|---|---|---|---|---|
| 1 | Australia | HIC | 1 | Nita Y, Batty KT, Plumridge RJ. Adverse drug reaction reporting: Attitudes of Australian hospital pharmacists and doctors. J Pharm Pract Res. 2005;35(1):9-14. |
| 2 | Brazil | UMIC | 2 | Botelho SF, Martins MAP, Vieira LB, Reis AMM. Post-marketing Safety Events Relating to New Drugs Approved in Brazil Between 2003 and 2013: A Retrospective Cohort Study. J Clin Pharmacol. 2017;57(4):493-9. |
| 3 | Canada | HIC | 3 | Lexchin J. Drug safety and health Canada. Int. J Risk Saf Med. 2010;22(1):41-53. |
| | | | 4 | Lexchin J. How safe and innovative are first-in-class drugs approved by health Canada: A cohort study. Healthcare Policy. 2016;12(2):65-75. |
| 4 | China | UMIC | 5 | Du W, Guo JJ, Jing Y, Li X, Kelton CM. Drug safety surveillance in China and other countries: a review and comparison. Value Health. 2008;11 Suppl 1:S130-6. |
| 5 | Japan | HIC | 6 | Hirayama K. Post-marketing safety administration in Japan. Ther Innov Regul Sci. 1994;28(2):421-6. |
| | | | 7 | Hirayama Y. Changing the review process: The view of the Japanese Ministry of Health and Welfare. Drug Inf J. 1998;32(1):111-7. |
| | | | 8 | Yamada T, Watanabe Y, Kusama M, Sugiyama Y, Ono S. Factors associated with spontaneous reporting of adverse drug reactions in Japan. Pharmacoepidemiol Drug Saf. 2013;22(5):468-76. |
| | | | 9 | Kanmuri K, Narukawa M. Characteristics of post-marketing studies and their contribution to post-marketing safety measures in Japan. Pharmaceut Med. 2014;28(2):67-73. |
| | | | 10 | Mori K, Watanabe M, Horiuchi N, Tamura A, Kutsumi H. The role of the Pharmaceuticals and Medical Devices Agency and healthcare professionals in post-marketing safety. Clin J Gastroenterol. 2014;7(2):103-7. |
| 6 | The Netherlands | HIC | 11 | van Grootheest AC, Groote JK, de Jong-van den Berg LT. Intensive monitoring of new drugs based on first prescription signals from pharmacists: a pilot study. Pharmacoepidemiol Drug Saf. 2003;12(6):475-81. |
| | | | 12 | Mol PGM, Straus SMJM, Piening S, De Vries JTN, De Graeff PA, Haaijer-Ruskamp FM. A decade of safety-related regulatory action in the Netherlands: A retrospective analysis of direct healthcare professional communications from 1999 to 2009. Drug Saf. 2010;33(6):463-74. |
| | | | 13 | Harmark L, van Grootheest K. Web-based intensive monitoring: from passive to active drug surveillance. Expert Opin Drug Saf. 2012;11(1):45-51. |

| No. | Countries | Level of income | No. | Articles |
|---|---|---|---|---|
| | | | 14 | Piening S, Haaijer-Ruskamp FM, de Graeff PA, Straus SM, Mol PG. Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. Drug Saf. 2012;35(11):1061-72. |
| 7 | New Zealand | HIC | 15 | Coulter DM. The New Zealand intensive medicines monitoring program in pro-active safety surveillance. Pharmacoepidemiol Drug Saf. 2000;9(4):273-80. |
| | | | 16 | Coulter DM. Privacy issues and the monitoring of sumatriptan in the New Zealand Intensive Medicines Monitoring Program. Pharmacoepidemiol Drug Saf. 2001;10(7):663-7. |
| 8 | Sweden | HIC | 17 | Ekman E, Backstrom M. Attitudes among hospital physicians to the reporting of adverse drug reactions in Sweden. Eur J Clin Pharmacol. 2009;65(1):43-6. |
| 9 | Thailand | UMIC | 18 | Amrumpai Y, Kiatying-Angsulee N, Chamroonsawasdi K. Identifying safety indicators of new drug Safety Monitoring Program (SMP) in Thailand. Drug Inf J 2007;41(6):769-77. |
| | | | 19 | Jarernsiripornkul N, Krska J, Pongmanachai M, Nasritha N. Hospital pharmacists' activities and attitudes regarding the Thai safety monitoring program for new drugs. Pharmacoepidemiol Drug Saf. 2009;18(9):837-41. |
| 10 | The United Kingdom | HIC | 20 | Inman WH. Post-marketing surveillance of adverse drug reactions in general practice. II: Prescription-event monitoring at the University of Southampton. Br Med J (Clin Res Ed). 1981;282(6271):1216-7. |
| | | | 21 | Buckley EG. Post-marketing surveillance of new drugs. J R Coll Gen Pract. 1987;37(301):337-8. |
| | | | 22 | Andrew JE, Prescott P, Smith TMF, Inman WHW, Kubota K. Testing for adverse reactions using prescription event monitoring. Stat Med. 1996;15(10):987-1002. |
| | | | 23 | Mackay FJ. Post-marketing studies: the work of the Drug Safety Research Unit. Drug Saf. 1998;19(5):343-53. |
| | | | 24 | Evans SJW, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10(6):483-6 |
| | | | 25 | Gough S. Post-marketing surveillance: a UK/European perspective. Curr Med Res Opin. 2005;21(4):565-70. |
| | | | 26 | Breckenridge A. Development and delivery of clinical pharmacology in regulatory agencies. Br J Clin Pharmacol. 2012;73(6):866-9. |
| | | | 27 | Layton D, Shakir SAW. Specialist Cohort Event Monitoring Studies: A New Study Method for Risk Management in Pharmacovigilance. Drug Saf. 2015;38(2):153-63. |

| No. | Countries | Level of income | No. | Articles |
|---|---|---|---|---|
| 11 | The United States | HIC | 28 | Faich GA. US adverse drug reaction surveillance 1989-1994. Pharmacoepidemiol Drug Saf. 1996;5(6):393-8. |
| | | | 29 | Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. JAMA. 2002;287(17):2215-20. |
| | | | 30 | Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. Arch Intern Med. 2007;167(16):1752-9. |
| | | | 31 | Moore TJ, Furberg CD. Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US food and drug administration the class of 2008. JAMA Intern Med. 2014;174(1):90-5. |
| | | | 32 | Pinnow E, Amr S, Bentzen SM, Brajovic S, Hungerford L, St. George DM, et al. Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014. Clin Pharm Therap. 2018;104(2):390-400. |
| | | | 33 | Brown WV, Bramlet DA, Ross JL, Underberg JA. JCL roundtable: Risk evaluation and mitigation strategy. J Clin Lipidol. 2016;10(6):1288-96. |
| | | | 34 | Fan Y, Sun B, Agarwal S, Zhang L. Review of Transporter-Related Post-marketing Requirement or Post-marketing Commitment Studies. J Clin Pharmacol. 2016: S193-S204. |
| | | | 35 | Mott K, Graham DJ, Toh S, Gagne JJ, Levenson M, Ma Y, et al. Uptake of new drugs in the early post-approval period in the Mini-Sentinel distributed database. Pharmacoepidemiol Drug Saf. 2016;25(9):1023-32. |
| | | | 36 | Mostaghim SR, Gagne JJ, Kesselheim AS. Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: Retrospective cohort study. BMJ (Online). 2017;358. |
| | | | 37 | Schick A, Miller KL, Lanthier M, Dal Pan G, Nardinelli C. Evaluation of Pre-marketing Factors to Predict Post-marketing Boxed Warnings and Safety Withdrawals. Drug Saf. 2017;40(6):497-503. |
| | | | 38 | Fukazawa C, Hinomura Y, Kaneko M, Narukawa M. Significance of data mining in routine signal detection: Analysis based on the safety signals identified by the FDA. Pharmacoepidemiol Drug Saf. 2018. |

## Appendix C-Scoping review from drug regulatory authority websites

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | Ministry of Health | NA | Pharmacovigilance system | 2008 | https://www.salut.ad/ https://www.salut.ad/RAM/ |
| 2 | Austria | HIC | Europe | Federal Ministry for Social Affairs, Health, Care and Consumer Protection of Austria | Federal Office for Safety in Health Care | Pharmacovigilance system | 1991 | https://www.basg.gv.at/ |
| 3 | Belgium | HIC | Europe | Federal Public Service | Federal Agency for Medicines and Health Products (FAMHP) | Belgian Center for Pharmacovigilance | 1977 | https://www.famhp.be/en |
| *4* | *Channel Island* | *HIC* | *Europe* | *NA* | *NA* | *NA* | *Non-WHO* | *https://www.gov.je/Health/Pages/default.aspx* |
| 5 | Croatia | HIC | Europe | Ministry of Health the Republic of Croatia | Agency for Medicinal Products and Medical Device of Croatia | Division for the Safe Use of Medicinal Products and Medical Devices | 1992 | http://www.halmed.hr/en/ |
| 6 | Cyprus | HIC | Europe | Ministry of Health Pharmaceutical Products | Pharmaceutical Services | Pharmacovigilance system | 2000 | https://www.moh.gov.cy/ https://www.moh.gov.cy/moh/phs/phs.nsf/home/home?openform |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 7 | Czech Republic | HIC | Europe | Ministry of Health the Czech Republic | State Institute for Drug Control | Department for Pharmacovigilance Branch | 1992 | http://www.sukl.eu/ http://www.sukl.eu/medicines/pharmacovigilance |
| 8 | Denmark | HIC | Europe | Danish Ministry of Health | Danish Medicines Agency | Pharmacovigilance and Medical Device Division | 1971 | https://laegemiddelstyrelsen.dk/ |
| 9 | Estonia | HIC | Europe | Ministry of Health Estonia | Republic of Estonia Agency of Medicines | Bureau of Pharmacovigilance | 1998 | https://www.ravimiamet.ee/en https://www.ravimiamet.ee/en/pharmacovigilance |
| *10* | *Faroe Islands* | *HIC* | *Europe* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.hmr.fo/en/* |
| 11 | Finland | HIC | Europe | Ministry of Social Affairs and Health | Finnish Medicines Agency | Fimea Supervision Pharmacovigilance | 1974 | https://www.fimea.fi/web/en https://www.fimea.fi/web/en/supervision/pharmacovigilance |
| 12 | France | HIC | Europe | Minister for Solidarity and Health | National Agency for the State of Medicine and Health Products | Pharmacovigilance system | 1986 | https://www.ansm.sante.fr/ |
| 13 | Germany | HIC | Europe | The Federal Ministry of Health Germany | The Federal Institute for Drugs and Medical Devices | Pharmacovigilance division | 1968 | https://www.bfarm.de/EN/ https://www.bfarm.de/EN/Drugs/vigilance |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *14* | *Gibraltar* | *HIC* | *Europe* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.gha.gi/about-us/ministry-for-health/* |
| 15 | Greece | HIC | Europe | Ministry of Health | National Organization for Medicines | Pharmacovigilance system | 1990 | http://www.eof.gr/ http://www.eof.gr/web/guest/pharmacovigilance |
| *16* | *Greenland* | *HIC* | *Europe* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://naalakkersuisut.gl//da/Naalakkersuisut/Departementer/Sundhed* |
| 17 | Hungary | HIC | Europe | Ministry of Health | National Institute of Pharmacy and Nutrition | Pharmacovigilance system | 1990 | https://ogyei.gov.hu/ https://ogyei.gov.hu/pharmacovigilance |
| 18 | Iceland | HIC | Europe | Ministry of Health Iceland | Icelandic Medicines Agency | Pharmacovigilance system | 1990 | http://www.imca.is/ https://www.ima.is/pharmacovigilance/ |
| 19 | Ireland | HIC | Europe | Department of Health Ireland | Health Products Regulatory Authority | Pharmacovigilance system | 1968 | https://www.hpra.ie/ http://www.hpra.ie/homepage/medicines/regulatory-information/pharmacovigilance-and-post-authorisation-safety |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *20* | *Isle of Man* | *HIC* | *Europe* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.gov.im/about-the-government/departments/health-and-social-care/* |
| 21 | Italy | HIC | Europe | Italian Ministry of Health | Italians Medicines Agency | Post-Marketing Supervision Area Pharmacovigilance | 1975 | https://www.aifa.gov.it/ |
| 22 | Latvia | HIC | Europe | Ministry of Health of the Republic of Latvia | State Agency of Medicines | Pharmacovigilance division | 2002 | https://www.zva.gov.lv/ |
| 23 | Liechtenstein | HIC | Europe | Ministry of Health | NA | Pharmacovigilance system | Non-WHO member | https://www.llv.li/inhalt/11134/amtsstellen/arzneimitteluberwachung |
| 24 | Lithuania | HIC | Europe | Ministry of Health of the Republic of Lithuania | State Medicines Control Agency | Pharmacovigilance system | 2005 | https://www.vvkt.lt/ |
| 25 | Luxembourg | HIC | Europe | Ministry Department of Health | Pharmacy and Medicines Division | Pharmacovigilance system | 2020 | https://sante.public.lu/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 26 | Malta | HIC | Europe | Malta Ministry of Health | Medicines Authority | Post-Licensing Directorate Pharmacovigilance | 2004 | http://www.medicinesauthority.gov.mt/ http://www.medicinesauthority.gov.mt/safety?l=1 |
| *27* | *Monaco* | *HIC* | *Europe* | *Ministry of Health and Social Affairs* | *NA* | *NA* | *Non-WHO member* | *https://en.gouv.mc/Government-Institutions/The-Government/Ministry-of-Health-and-Social-Affairs* |
| 28 | The Netherlands | HIC | Europe | Ministry of Health | Medicines Evaluation Board | LAREB National Pharmacovigilance Center | 1968 | https://www.cbg-meb.nl/ https://www.lareb.nl/ |
| 29 | Norway | HIC | Europe | The Royal Norwegian Ministry of Health and Care Services | Norwegian Medicines Agency | Unit for Pharmacovigilance | 1971 | https://legemiddelverket.no/English https://legemiddelverket.no/english/pharmacovigilance |
| 30 | Poland | HIC | Europe | Ministry of Health of the Republic of Poland | National Medicines Institute | Pharmacovigilance system | 1972 | http://urpl.gov.pl/en/office http://www.nil.gov.pl/ |
| 31 | Portugal | HIC | Europe | Ministry of Health | National Authority of Medicines and Medicinal Products | Drug Risk Management Director | 1993 | https://www.infarmed.pt/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 32 | Romania | HIC | Europe | Romania Ministry of Health | National Authority and Medical Devices | Pharmacovigilance system | 1976 | https://www.anm.ro/ https://www.anm.ro/en/medicamente-de-uz-uman/farmacovigilenta/ |
| *33* | *San Marino* | *HIC* | *Europe* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |
| 34 | Slovakia | HIC | Europe | Ministry of Health of the Republic of Slovakia | State Institute for Drug Control | Pharmacovigilance system | 1993 | https://www.sukl.sk/ |
| 35 | Slovenia | HIC | Europe | Ministry of Health Slovenia | Agency for Medicine Products and Medical Devices | Pharmacovigilance system | 2010 | http://www.jazmp.si/ https://www.jazmp.si/humana-zdravila/farmakovigilanca/ |
| 36 | Spain | HIC | Europe | Ministry of Health | Spanish Agency for Medicines and Health Products | Pharmacovigilance system | 1984 | https://www.aemps.gob.es/ https://www.aemps.gob.es/medicamentos-de-uso-humano/farmacovigilancia-de-medicamentos-de-uso-humano/ |
| 37 | Sweden | HIC | Europe | Ministry of Health and Social Affairs | Swedish Medical Products Agency | Pharmacovigilance system | 1968 | https://www.lakemedelsverket.se/sv |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 38 | Switzerland | HIC | Europe | Federal Office of Public Health | Swiss Medic | Pharmacovigilance system | 1991 | https://www.swissmedic.ch/ |
| 39 | The United Kingdom | HIC | Europe | Department of Health and Social care | Medicines and Health Products Regulatory Agency | Vigilance and Risk Management of Medicine Division | 1968 | https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency |
| *40* | *Bermuda* | *HIC* | *North America* | *Ministry of Health* | *NA* | *NA* | *Non-WHO* | *https://www.gov.bm/ministry/health* |
| 41 | Canada | HIC | North America | Health Ministry of Canada | Health Product and Food Branch | Marketed Health Product Directorate | 1968 | https://www.canada.ca/en/health-canada/services/drugs-health-products.html |
| 42 | The United States | HIC | North America | United States Department of Health and Human Services | United States Food and Drug Administration | Office of Surveillance and Epidemiology | 1968 | https://www.fda.gov/safety/ |
| *43* | *Antigua and Barbuda* | *HIC* | *Caribbean* | *Ministry of Health, Wellness and Environment* | *NA* | *NA* | *Non-WHO member* | *https://ab.gov.ag/detail_page.php?page=29* |
| *44* | *Aruba* | *HIC* | *Caribbean* | *Ministry of Public Health* | *NA* | *NA* | *Non-WHO member* | *No website* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *45* | *Bahamas* | *HIC* | *Caribbean* | *Ministry of Health the Bahamas* | *National Drug Agency* | *NA* | *Non-WHO member* | *https://www.bahamas.gov.bs/ http://www.phabahamas.org/hospitals_services_bnda.php* |
| 46 | Barbados | HIC | Caribbean | Ministry of Health and Wellness | Barbados Drug Service | Pharmacovigilance system (CARPHA group) | 2008 | http://drugservice.gov.bb/ |
| *47* | *British Virgin Islands* | *HIC* | *Caribbean* | *Ministry of Health and Social Development* | *NA* | *NA* | *Non-WHO member* | *https://bvi.gov.vg/content/ministry-health-and-social-development* |
| *48* | *Cayman Islands* | *HIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.ministryofhealth.gov.ky/* |
| 49 | Chile | HIC | Latin America | Ministry of Health Chile | Institute of Public Health of Chile | National Center for Medicines and Pharmacovigilance Information | 1996 | http://www.ispch.cl/farmacovigilancia |
| *50* | *Curaçao* | *HIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://gobiernu.cw/ (Non-English)* |
| 51 | Panama | HIC | Latin America | Ministry of Health Panama | National Directorate of Pharmacy and Drugs | National Pharmacovigilance Center | 2016 | http://www.minsa.gob.pa/ http://www.minsa.gob.pa/contenido/departamento-de-farmacovigilancia-0 |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *52* | *Puerto Rico* | *HIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.salud.gov.pr/Pages/Home.aspx* |
| *53* | *Saint Maarten (Dutch part)* | *HIC* | *Caribbean* | *Ministry of Public Health* | *NA* | *NA* | *Non-WHO member* | *http://www.sintmaartengov.org/government/VSA/Pages/default.aspx* |
| *54* | *Saint Kitts and Nevis* | *HIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.gov.kn/moh* |
| *55* | *Saint Martin (French part)* | *HIC* | *Caribbean* | *NA* | *NA* | *NA* | *Non-WHO member* | *No website* |
| 56 | Trinidad and Tobago | HIC | Caribbean | Ministry of Health | Chemistry, Food and Drug division | Pharmacovigilance system (CARPHA group) | Non-WHO member | http://www.health.gov.tt/sitepages/default.aspx?id=93 |
| *57* | *Turks and Caicos Islands* | *HIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.gov.tc/moh/* |
| 58 | Uruguay | HIC | Latin America | Ministry of Public Health Uruguay | NA | Pharmacovigilance system | 2001 | https://www.gub.uy/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *59* | *Virgin Islands (U.S.)* | *HIC* | *Caribbean* | *United States Virgin Islands Department of Health* | *NA* | *NA* | *Non-WHO member* | *https://doh.vi.gov/* |
| 60 | Australia | HIC | Asia | Department of Health | Therapeutic Goods Administration | Pharmacovigilance and special access | 1968 | https://www.tga.gov.au/ |
| 61 | Brunei Darussalam | HIC | Asia | Ministry of Health Brunei | Drug Administration Section | National Adverse Drug Reaction Monitoring Center | 2005 | http://www.moh.gov.bn/ |
| *62* | *French Polynesia* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.presidence.pf/* |
| *63* | *Guam* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |
| 64 | Hong Kong | HIC | Asia | Ministry of Health | Drug office | Pharmacovigilance system | Non-WHO member | https://www.drugoffice.gov.hk/ |
| 65 | Japan | HIC | Asia | Ministry of Health Labor and Welfare | Pharmaceutical and Medicals Devices Agency | Pharmacovigilance division | 1972 | https://www.mhlw.go.jp/ https://www.pmda.go.jp/english/ |
| 66 | Korea (South) | HIC | Asia | Ministry of Health and Welfare | Korean Food and Drug Administration (KFDA) | Korean Institute of Drug Safety & Risk Management (KIDS) | 1992 | https://www.mfds.go.kr/ https://www.drugsafe.or.kr/en/index.do |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *67* | *Macao* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.ssm.gov.mo/portal/ (Non-English)* |
| *68* | *Nauru* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |
| 69 | New Caledonia | HIC | Asia | Ministry of Health | NA | Pharmacovigilance system | Non-WHO member | https://dass.gouv.nc/ |
| 70 | New Zealand | HIC | Asia | New Zealand Ministry of Health | Med Safe | New Zealand pharmacovigilance center (NZPhvC) | 1968 | https://www.medsafe.govt.nz/ |
| *71* | *Northern Mariana Islands* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |
| *72* | *Palau* | *HIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.palauhealth.org/* |
| 73 | Singapore | HIC | Asia | Ministry of Health Singapore | Health Science Authority | Pharmacovigilance units | 1993 | https://www.hsa.gov.sg/ |
| 74 | Taiwan | HIC | Asia | Ministry of Health | Taiwan Food and Drug Administration | Pharmacovigilance system | Non-WHO member | https://www.fda.gov.tw/ENG/ |
| *75* | *Bahrain* | *HIC* | *Arab* | *Ministry of Health* | *National Health Regulatory Authority* | *NA* | *Non-WHO member* | *https://www.nhra.bh/ https://www.nhra.bh/Departments/PPR/* |
| 76 | Israel | HIC | Arab | Israel Ministry of Health | NA | Pharmacovigilance and Drug Information Department | 1973 | https://www.health.gov.il/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *77* | *Kuwait* | *HIC* | *Arab* | *Ministry of Health* | *Food and Drug Control* | *NA* | *Non-WHO member* | *No website* |
| 78 | Oman | HIC | Arab | Ministry of Health | NA | Department of Pharmacovigilance and Drug Information (DPV&DI) | 1995 | https://www.moh.gov.om/ |
| *79* | *Qatar* | *HIC* | *Arab* | *Ministry of Health* | *Pharmacy and Drug Control Department* | *NA* | *Non-WHO member* | *https://www.moph.gov.qa/english/derpartments/policyaffairs/pdc/Pages/default.aspx* |
| 80 | Saudi Arabia | HIC | Arab | Saudi Arabia Ministry of Health | Saudi Food and Drug Authority (SFDA) | National Pharmacovigilance Center | 2009 | https://www.sfda.gov.sa/en https://www.sfda.gov.sa/en/pharmacovigilance |
| 81 | The United Arab Emirates | HIC | Arab | The Ministry of Health and Prevention | NA | Pharmacovigilance system (Drug Control Department) | 2013 | https://www.mohap.gov.ae/ |
| 82 | Mauritius | HIC | Arab | Ministry of Health and Wellness | NA | Pharmacovigilance system | 2014 | http://health.govmu.org/ |
| *83* | *Seychelles* | *HIC* | *Arab* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.health.gov.sc/* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 84 | Albania | UMIC | Europe | Ministry of Health | National agency for drugs and medical devices | Pharmacovigilance | Non-WHO member | http://akbpm.gov.al/sektori-i-farmakovigjilences/ |
| 85 | Armenia | UMIC | Europe | The Republic of Armenia Ministry of Health | Scientific Center of Drug and Medical Technology | Pharmacovigilance department | 2001 | http://www.pharm.am/index.php/en/pharmacovigilance-department |
| 86 | Azerbaijan | UMIC | Europe | Ministry of Health of the Republic of Azerbaijan | Analytical Expertise Center | Pharmacovigilance system | 2018 | http://www.pharma.az/ http://www.pharma.az/index.php?lang=3&ind=main&id=62 |
| 87 | Belarus | UMIC | Europe | The Ministry of Health of the Republic of *Belarus* | Center for examinations and tests in health service | Pharmacovigilance system | 2006 | https://www.rceth.by/en/Departments/Unfp https://www.rceth.by/Reaction |
| 88 | Bosnia and Herzegovina | UMIC | Europe | Federal Ministry of Health Bosnia and Herzegovina | The Agency for Medicinal Products and Medical Devices | Pharmacovigilance system | 2019 | http://www.almbih.gov.ba/ http://www.almbih.gov.ba/en/vigilance/ |
| 89 | Bulgaria | UMIC | Europe | Ministry of Health Republic of Bulgarian | Bulgarian Drug Agency | Pharmacovigilance division | 1975 | https://www.bda.bg/bg/ |
| *90* | *Georgia* | *UMIC* | *Europe* | *Ministry of Health, Labor and Social Affairs of Georgia* | *NA* | *NA* | *2018* | *https://moh.gov.ge/en/ministry/* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 91 | Kazakhstan | UMIC | Europe | Ministry of Healthcare Kazakhstan | National for expert evaluation of medicinal product, medical devices and medical equipment | Pharmacovigilance system | 2008 | https://www.ndda.kz/ |
| *92* | *Kosovo* | *UMIC* | *Europe* | *Ministry of Health* | *Kosovo Medicine Agency* | *NA* | *Non-WHO member* | *https://akppm.rks-gov.net/ (Non-English)* |
| 93 | Montenegro | UMIC | Europe | Ministry of Health Montenegro | National Agency for Medicines and Medical Devices (CALIMS) | Pharmacovigilance department | 2009 | https://www.calims.me/ |
| 94 | North Macedonia | UMIC | Europe | Ministry of Health | Agency for Medicinal Products and Medical devices | Pharmacovigilance system | 2000 | https://lekovi.zdravstvo.gov.mk/pharmacovigilances |
| 95 | Russia | UMIC | Europe | Ministry of Health Russian | Federal Services for Surveillance in Healthcare | Pharmacovigilance system | 1998 | https://roszdravnadzor.gov.ru/en |
| 96 | Serbia | UMIC | Europe | Ministry of Health Serbia | Medicines and Medical Devices Agency of Serbia | National Pharmacovigilance Center | 2000 | https://www.alims.gov.rs/eng/ https://www.alims.gov.rs/eng/pharmacovigilance/ |
| 97 | Turkey | UMIC | Europe | Ministry of Health Turkey | Turkish Medicines and Medical Devices Agency | Turkish Pharmacovigilance Center | 1987 | https://www.titck.gov.tr/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *98* | *Turkmenistan* | *UMIC* | *Europe* | *Ministry of Health* | *Drug Regulatory Authority* | *NA* | *Non-WHO member* | *http://www.saglykhm.gov.tm/app/home* |
| 99 | Argentina | UMIC | Latin America | Ministry of Health Argentina | National of Administration of Drugs, Food and Medical Devices | Pharmacovigilance system | 1994 | https://www.argentina.gob.ar/anmat https://www.argentina.gob.ar/anmat/farmacovigilancia |
| 100 | Belize | UMIC | Caribbean | Ministry of Health Belize | NA | VigiCarib-ADR reporting (CARPHA group) | Non-WHO member | https://www.health.gov.bz/ |
| 101 | Brazil | UMIC | Latin America | Ministry of Health Brazilian | Brazilian Health Surveillance Agency (ANVISA) | Pharmacovigilance system | 2001 | http://portal.anvisa.gov.br/ |
| 102 | Colombia | UMIC | Latin America | Ministry of Health and Social Protection | The Columbia National Food and Drug Surveillance | Pharmacovigilance system | 2004 | https://www.invima.gov.co/ |
| 103 | Costa Rica | UMIC | Latin America | Ministry of Health Costa Rica | NA | National Pharmacovigilance Center | 1991 | https://www.ministeriodesalud.go.cr/ |
| 104 | Cuba | UMIC | Latin America | Ministry of Public Health Cuba | Directorate of Medicines and Medical Technology | Department of Surveillance | 1994 | https://www.cecmed.cu/ https://www.cecmed.cu/vigilancia |
| *105* | *Dominica* | *UMIC* | *Caribbean* | *Ministry of Health, Wellness, and New Health Investment* | *NA* | *NA* | *Non-WHO member* | *http://health.gov.dm/* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 106 | Dominican Republic | UMIC | Latin America | Ministry of Health and Environment | NA | Pharmacovigilance system | 2020 | https://www.dominicanasolidaria.org/ |
| *107* | *Ecuador* | *UMIC* | *Latin America* | *Ministry of Public Health Ecuador* | *National Agency for Regulation, Control and Surveillance* | *NA* | *2017* | *https://www.controlsanitario.gob.ec/tecnovigilancia-farmacovigilancia/ (Non-English)* |
| *108* | *Grenada* | *UMIC* | *Caribbean* | *Ministry of Health* | *Medicine Regulatory Authority* | *NA* | *Non-WHO member* | *http://www.gov.gd/moh/* |
| 109 | Guatemala | UMIC | Latin America | Guatemala Ministry of Health and Social Assistance | NA | Office of Pharmacovigilance | 2002 | https://www.mspas.gob.gt/ https://medicamentos.mspas.gob.gt/index.php/formularios/farmacovigilancia |
| *110* | *Guyana* | *UMIC* | *Caribbean* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.health.gov.gy/* |
| 111 | Jamaica | UMIC | Caribbean | Ministry of Health and Wellness | The Standard and Regulation Division | National Pharmacovigilance Center | 2012 | https://www.moh.gov.jm/divisions-agencies/divisions/standards-and-regulation-division/pharmacovigilance/ |
| 112 | Mexico | UMIC | Latin America | Ministry of Health Mexico | COFEPRIS | Pharmacovigilance system | 1999 | https://www.gob.mx/cofepris |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *113* | *Paraguay* | *UMIC* | *Latin America* | *Ministry of Health* | *NA* | *NA* | *2018* | *https://www.mspbs.gov.py/index.php* |
| 114 | Peru | UMIC | Latin America | Ministry of Health Peru | General Directorate of Medicines, Supplied and Drugs | Pharmacovigilance department | 2001 | http://www.digemid.minsa.gob.pe/ |
| *115* | *Saint. Lucia* | *UMIC* | *Caribbean* | *Ministry of Health Lucia* | *NA* | *NA* | *Non-WHO member* | *http://health.govt.lc/* |
| *116* | *Saint. Vincent and the Grenadines* | *UMIC* | *Caribbean* | *Ministry of Health Wellness and Environment* | *Pharmaceutical services* | *NA* | *2020* | *http://health.gov.vc/health/index.php/pharmaceutical-services* |
| *117* | *Suriname* | *UMIC* | *Caribbean* | *Ministry of Health Suriname* | *NA* | *NA* | *2007* | *http://health.gov.sr/* |
| 118 | Venezuela, RB | UMIC | Latin America | Ministry of Popular Power for Health | NA | National Center for Pharmaceutical Surveillance | 1995 | http://www.inhrr.gob.ve/ http://www.inhrr.gob.ve/sistema_nacional_farmacovigilancia_ce.php |
| *119* | *American Samoa* | *UMIC* | *Asia* | *Department of Public Health* | *NA* | *NA* | *Non-WHO member* | *https://www.americansamoa.gov/department-of-public-health* |
| 120 | China | UMIC | Asia | National Health Commission | National Medical Products Administration (NMPA) | China Adverse Drug Reaction Monitoring System | 1998 | http://english.nmpa.gov.cn/ |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| *121* | *Fiji* | *UMIC* | *Asia* | *Ministry of Health* | *Medicines Regulatory Authority* | *NA* | *1999* | *http://www.health.gov.fj/* |
| 122 | Indonesia | UMIC | Asia | Ministry of Health Indonesia | The National Agency of Drug and Food Control | Pharmacovigilance Unit | 1990 | https://www.pom.go.id/ |
| 123 | Malaysia | UMIC | Asia | Ministry of Health Malaysia | National Pharmaceutical Regulatory Agency | National Center for Adverse Drug Reaction Monitoring | 1990 | https://npra.gov.my/ |
| *124* | *Maldives* | *UMIC* | *Asia* | *Ministry of Health Maldives* | *Maldives Food and Drug Administration* | *NA* | *2016* | *No website* |
| *125* | *Marshall Islands* | *UMIC* | *Asia* | *Ministry of Health* | *Medicines Regulatory Authority* | *NA* | *Non-WHO member* | *http://rmihealth.org/* |
| *126* | *Samoa* | *UMIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *https://www.samoagovt.ws/minister-moh/* |
| 127 | Thailand | UMIC | Asia | Ministry of Public Health Thailand | Thai Food and Drug Administration | Health Product Vigilance Center | 1984 | http://www.fda.moph.go.th/ http://thaihpvc.fda.moph.go.th/ |
| *128* | *Tonga* | *UMIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.health.gov.to/* |
| *129* | *Tuvalu* | *UMIC* | *Asia* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 130 | Iran | UMIC | Arab | Iran Ministry of Health | Iran Food and Drug Administration | Pharmacovigilance system | Non-WHO member | https://www.fda.gov.ir/en |
| 131 | Iraq | UMIC | Arab | Iraqi Ministry of Health | NA | Iraqi Pharmacovigilance Center (IPC) | 2010 | https://moh.gov.iq/ |
| 132 | Jordan | UMIC | Arab | Jordan Ministry of Health | The Jordanian Food and Drug Administration (JFDA) | Rational Drug Use and Pharmacovigilance Department | 2002 | http://www.jfda.jo/ http://www.jfda.jo/Pages/viewpage.aspx?pageID=173 |
| *133* | *Lebanon* | *UMIC* | *Arab* | *Ministry of Public Health* | *Pharmaceutical* | *NA* | *Non-WHO member* | *https://www.moph.gov.lb/en https://www.moph.gov.lb/en/Pages/3/3010/pharmaceuticals* |
| *134* | *Libya* | *UMIC* | *Arab* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://health.gov.ly* |
| 135 | Botswana | UMIC | Africa | Ministry of Health and Wellness | Medicine Regulatory Authority | Pharmacovigilance Center | 2009 | https://www.bomra.co.bw/ https://www.bomra.co.bw/index.php/services/patient-safety-monitoring |
| *136* | *Equatorial Guinea* | *UMIC* | *Africa* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *No website* |
| *137* | *Gabon* | *UMIC* | *Africa* | *Ministry of Health* | *NA* | *NA* | *Non-WHO member* | *http://www.sante.gouv.ga/* |

| No. | Countries | Level of income | Region | Health Ministry | Drug regulatory authorities | Pharmacovigilance center/ Pharmacovigilance system | WHO member | Drug regulatory authority websites |
|---|---|---|---|---|---|---|---|---|
| 138 | Namibia | UMIC | Africa | Ministry of Health and Population | Namibia Medicine Regulatory Council | Therapeutic Information Pharmacovigilance Center | 2008 | https://nmrc.gov.na/ https://nmrc.gov.na/tipc1 |
| 139 | South Africa | UMIC | Africa | National Department of Health | Health Products Regulatory Authority | National Adverse Drug Event Monitoring Center | 1992 | https://www.sahpra.org.za/ https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA |

: NA (not available)

: Countries with italic had no information on pharmacovigilance system of new drugs

: CARPHA (the Caribbean public health agency)

## Appendix D-PV guideline

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | | |
| 2 | Austria | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 3 | Belgium | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 4 | Croatia | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 5 | Cyprus | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 6 | Czech Republic | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 7 | Denmark | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 8 | Estonia | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 9 | Finland | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 10 | France | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 11 | Germany | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 12 | Greece | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 13 | Hungary | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 14 | Iceland | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 15 | Ireland | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 16 | Italy | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 17 | Latvia | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 18 | Liechtenstein | HIC | Europe | | |
| 19 | Lithuania | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 20 | Luxembourg | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 21 | Malta | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 22 | Netherland | HIC | Europe | Guideline on EU GVP | 2012-2013 |

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 23 | Norway | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 24 | Poland | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 25 | Portugal | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 26 | Romania | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 27 | Slovakia | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 28 | Slovenia | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 29 | Spain | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 30 | Sweden | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 31 | Switzerland | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 32 | The United Kingdom | HIC | Europe | Guideline on EU GVP | 2012-2013 |
| 33 | Canada | HIC | North America | Guideline on reporting adverse reactions for the MAHs | 2018 |
| 34 | The United States | HIC | North America | -Best Practice in Drug and Biological Product Post Marketing Safety Surveillance for FDA staff<br>-GVP for industry | 2019<br>2005 |
| 35 | Barbados | HIC | Caribbean | | |
| 36 | Chile | HIC | Latin America | | |
| 37 | Panama | HIC | Latin America | Manual Good Pharmacovigilance Practices | 2019 |
| 38 | Trinidad and Tobago | HIC | Caribbean | | |

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 39 | Uruguay | HIC | Latin America | | |
| 40 | Australia | HIC | Asia | Pharmacovigilance responsibilities sponsors | 2018 |
| 41 | Brunei Darussalam | HIC | Asia | Pharmacovigilance guideline | 2018 |
| 42 | Hong Kong | HIC | Asia | Guideline for Industry-Adverse drug reporting requirement | 2019 |
| 43 | Japan | HIC | Asia | Pharmaceutical Administration and Regulation | 2020 |
| 44 | Korea (South) | HIC | Asia | Regulation on Safety of Pharmaceutical | 2019 |
| 45 | New Caledonia | HIC | Asia | | |
| 46 | New Zealand | HIC | Asia | Regulation of therapeutic products in New Zealand part 8: pharmacovigilance | 2017 |
| 47 | Singapore | HIC | Asia | Guidance for industry post-marketing vigilance requirement for therapeutic products | 2020 |
| 48 | Taiwan | HIC | Asia | ICH guideline | |
| 49 | Israel | HIC | Arab | Reporting Adverse Event and New Safety | 2013 |

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 50 | Oman | HIC | Arab | Guideline on GVP in Oman for MAHs/Pharmaceutical Companies | 2017 |
| 51 | Saudi Arabia | HIC | Arab | Guidelines on Good Pharmacovigilance Practices | 2015 |
| 52 | The United Arab Emirates | HIC | Arab | Guideline in Good Vigilance Practice | 2017 |
| 53 | Mauritius | HIC | Arab | Mauritius Guideline for Pharmacovigilance -ICH | 2003 |
| 54 | Albania | UMIC | Europe | | |
| 55 | Armenia | UMIC | Europe | Armenia-Pharmacovigilance guideline for MAH in Armenia | 2019 |
| 56 | Azerbaijan | UMIC | Europe | | |
| 57 | Belarus | UMIC | Europe | | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | | |
| 59 | Bulgaria | UMIC | Europe | Guideline on EU-GVP | 2012-2013 |
| 60 | Kazakhstan | UMIC | Europe | | |
| 61 | Montenegro | UMIC | Europe | | |
| 62 | North Macedonia | UMIC | Europe | | |
| 63 | Russia | UMIC | Europe | Guideline on EAEU-GVP | 2016 |

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 64 | Serbia | UMIC | Europe | Instruction for marketing authorization holders | |
| 65 | Turkey | UMIC | Europe | ICH guideline | |
| 66 | Argentina | UMIC | Latin America | | |
| 67 | Belize | UMIC | Caribbean | | |
| 68 | Brazil | UMIC | Latin America | ICH-guideline | |
| 69 | Colombia | UMIC | Latin America | | |
| 70 | Costa Rica | UMIC | Latin America | | |
| 71 | Cuba | UMIC | Latin America | | |
| 72 | Dominican Republic | UMIC | Latin America | | |
| 73 | Guatemala | UMIC | Latin America | | |
| 74 | Jamaica | UMIC | Caribbean | | |
| 75 | Mexico | UMIC | Latin America | | |
| 76 | Peru | UMIC | Latin America | | |
| 77 | Venezuela, RB | UMIC | Latin America | | |
| 78 | China | UMIC | Asia | ICH-guideline | |
| 79 | Indonesia | UMIC | Asia | | |
| 80 | Malaysia | UMIC | Asia | Malaysian Pharmacovigilance Guideline | 2016 |
| 81 | Thailand | UMIC | Asia | Safety Monitoring Program regulation | 2017 |
| 82 | Iran | UMIC | Arab | | |

| No. | Countries | Level of income | Region | PV guideline | Updated year of PV guideline |
|---|---|---|---|---|---|
| 83 | Iraq | UMIC | Arab | Guidelines for the National Pharmacovigilance System in Iraq | 2012 |
| 84 | Jordan | UMIC | Arab | Pharmacovigilance regulation | 2014 |
| 85 | Botswana | UMIC | Africa | Pharmacovigilance guideline | 2017 |
| 86 | Namibia | UMIC | Africa | National guideline for medicine safety surveillance | 2011 |
| 87 | South Africa | UMIC | Africa | Reporting Adverse Drug Reaction | 2020 |

## Appendix E-Authorized drug product database

| No. | Countries | Level of income | Region | Authorized drug product database | URL link | Contents | Download file of drug information |
|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | x | x | x | x |
| 2 | Austria | HIC | Europe | / | Medicinal specialties register: Searchable database<br>https://www.basg.gv.at/<br>https://aspregister.basg.gv.at/aspregister/faces/aspregister.jspx;jsessionid=LWZcoISPw-SFVOiYn7DuqHx-O6gOwINvVRqJyYWygawUImwdSjfA!41453725 | : Designation (product name)<br>: Approval number<br>: Owner<br>: Date of approval<br>: Active ingredients | : Professional information |
| 3 | Belgium [a] | HIC | Europe | / | Medicinal products database<br>https://banquededonneesmedicaments.afmps-fagg.be/#/query/human/ | : Name<br>: Pharmaceutical form<br>: Commercialized in Belgium<br>: Temporary supply problem<br>: Active substance<br>: Authorization holder<br>: Black triangle symbol-additional monitoring | : Leaflet<br>: SPC<br>: RMA<br>: DHPC |
| 4 | Croatia | HIC | Europe | / | Medicinal products database<br>https://www.halmed.hr/en/Lijekovi/Baza-lijekova/ | : Name, active substance<br>: Prescription<br>: Type of prescription<br>: Distribution/ATC code<br>: Medicinal product marketed in Croatia | : Educational materials for healthcare professionals<br>: Educational materials for patients/caregivers<br>: DHPC |

| No. | Countries | Level of income | Region | Authorized drug product database | URL link | Contents | Download file of drug information |
|---|---|---|---|---|---|---|---|
| 5 | Cyprus | HIC | Europe | x | x | x | x |
| 6 | Czech Republic | HIC | Europe | / | Medicinal products database<br>https://www.sukl.eu/modules/medication/search.php | : Medicinal product code<br>: Registration number<br>: ATC group<br>: Marketing authorization status | : SPC<br>: Supplement PIL |
| 7 | Denmark | HIC | Europe | / | Lists of medicines (Excel file update daily)<br>https://laegemiddelstyrelsen.dk/da/bivirkninger/find-medicin/lister-med-medicin/ | : Product name, pharmaceutical form, strength, active substances<br>: Manufacturer, ATC code, approved procedure (e.g. centralization)<br>: Registration date | x |
| 8 | Estonia | HIC | Europe | / | Medicinal products authorized in Estonia<br>https://www.ravimiregister.ee/en/publichomepage.aspx | : ATC code<br>: Active substance<br>: Dosage form<br>: Strength | x |

| No. | Countries | Level of income | Region | Authorized drug product database | URL link | Contents | Download file of drug information |
|---|---|---|---|---|---|---|---|
| 9 | Finland | HIC | Europe | / | Database and register https://www.fimea.fi/web/en/databases_and_registers | : Product name<br>: Marketing authorization holder<br>: Shortage, ATC code, strength, prescription status, pharmaceutical form, active substance, package size<br>: Type (such as medicinal product for human use), MA-status, MA number, MA date, prescription term, Type of products (such as biologic product) | : Link to EU-package leaflet<br>: Link to EU-SPC |
| 10 | France | HIC | Europe | / | Public drug database https://base-donnees-publique.medicaments.gouv.fr/ | : Therapeutic indications<br>: Generic group<br>: Composition of active substance<br>: Presentation (CIP code, marketing declaration, free price, non-reimbursable drug), actual benefit<br>: Authorization holders<br>: Prescription and dispensing conditions<br>: Authorization status<br>: Type of procedure (such as centralized procedure) | x |

| No. | Countries | Level of income | Region | Authorized drug product database | URL link | Contents | Download file of drug information |
|---|---|---|---|---|---|---|---|
| 11 | Germany | HIC | Europe | x | x | x | x |
| 12 | Greece | HIC | Europe | x | x | x | x |
| 13 | Hungary | HIC | Europe | / | Drug database<br>https://ogyei.gov.hu/gyogyszeradatbazis | : Registration number<br>: Active substance<br>: ACT code<br>: Marketing authorization holder<br>: Legal basis<br>: Registration status<br>: Date of authorization | : Link to accompany EMA document-EPAR |
| 14 | Iceland [a] | HIC | Europe | / | Medicinal product information<br>https://www.serlyfjaskra.is/# | : Drug name<br>: Pharmaceutical form/strength<br>: Category (medicine for men)<br>: ATC code<br>: Marketing authorization holder<br>: Special monitoring-black triangle | : Link to EPAR full text |
| 15 | Ireland | HIC | Europe | / | Medicines information<br>https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?showadv=true&list=HM | : Tradename<br>: License number<br>: Marketing authorization holder | : SPC, PIL, EPAR link to EMA |
| No. | Countries | Level of income | Region | Authorized drug product database | URL link | Contents | Download file of drug information |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 16 | Italy | HIC | Europe | / | Medicine database<br>https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/ | : Product name, active principles, packaging, registration number<br>: State (e.g. authorized) | : SPC |
| 17 | Latvia | HIC | Europe | / | Register of medicinal products<br>https://www.zva.gov.lv/zvais/zalu-registrs/?lang=lv | : Active substance<br>: Name of medicinal products<br>: Pharmaceutical form<br>: Strength/Concentration<br>: ATC code | x |
| 18 | Liechtenstein | HIC | Europe | x | x | x | x |
| 19 | Lithuania [a] | HIC | Europe | / | Search for medicines<br>https://vapris.vvkt.lt/vvkt-web/public/medications | : Name of preparation, active substance, strength, pharmaceutical form, method of administration, ATC code<br>: Registrant<br>: Date of registration<br>: Stage (registration)<br>: Application type<br>: Basis of supply to the market of the Republic of Lithuania (central registration)<br>: Black triangle symbol-medicines under additional monitoring | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |

| 20 | Luxembourg | HIC | Europe | x | x | x | x |
|---|---|---|---|---|---|---|---|
| 21 | Malta | HIC | Europe | / | National medicines<br>http://www.medicinesauthority.gov.mt/<br>http://www.medicinesauthority.gov.mt/advanced-search | : Product name, ATC code, active ingredients, pharmaceutical form, therapeutic class, classification, status (authorized),<br>: License number in the source country<br>: Authorization number<br>: Authorization date<br>: Authorization holder name<br>: Authorization holder address | : Product information-PIL, SPC |
| 22 | The Netherlands [a] | HIC | Europe | / | Drug information bank<br>https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:1:0::NO:RP,1:P0_DOMAIN,P0_LANG:H,NL | : Registration number, product name, ATC code, active ingredient<br>: Marketing authorization details (registration number, date of issue of marketing authorization)<br>: Black triangle-This medicine is under extra supervision | : SPC, PIL and link to EPAR |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 23 | Norway | HIC | Europe | / | Drug search<br>https://www.legemiddelsok.no/sider/default.aspx?f=Han;Vir;;Ikk;Mar;Avr;gen;par;&pane=0<br>Lists of new marketing authorization monthly<br>https://legemiddelverket.no/godkjenning/godkjenning-av-legemidler/liste-over-nye-markedsforingstillatelser | : Product name, dosage form, strength, volume, preparation<br>: Active ingredient<br>: Marketing authorization holder | x |
| 24 | Poland | HIC | Europe | x | x | x | x |
| 25 | Portugal | HIC | Europe | / | Medicine database<br>https://extranet.infarmed.pt/INFOMED-fo/ | : Drug name, active substance, pharmaceutical form, dosage<br>: Marketing authorization holder | : SPC, leaflet link to EPAR |
| 26 | Romania | HIC | Europe | / | Up to date results-Evaluation of drug authorization (PDF file)<br>https://www.anm.ro/medicamente-de-uz-uman/rezultate-la-zi-evaluare-autorizare-medicamente/ | : Product name, strength, pharmaceutical form, active ingredient<br>: Marketing authorization holder<br>: Status | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 27 | Slovakia | HIC | Europe | / | Database of registered medicine https://www.sukl.sk/hlavna-stranka/slovenska-verzia/databazy-a-servis/vyhladavanie-liekov-zdravotnickych-pomocok-a-zmien-v-liekovej-databaze/vyhladavanie-v-databaze-registrovanych-liekov?page_id=242 | : Registration number, active substance, package (e.g. single dose), condition (e.g. E-EU registration)<br>: Type of registration (European)<br>: Holder, country<br>: Indication group, ATC code<br>: Dispensing of drug (e.g. prescription-bound), approval date | : SPC and PIL link to EPAR |
| 28 | Slovenia | HIC | Europe | / | Central medicine database http://www.cbz.si/cbz/bazazdr2.nsf/Search/$searchForm?SearchView | : Name of medicinal product<br>: Packing, pharmaceutical form<br>: ATC code, mode, legal status<br>: Marketing authorization holder | x |
| 29 | Spain [a] | HIC | Europe | / | Drug information center https://cima.aemps.es/cima/publico/home.html | : Marketing authorization number<br>: Authorized marketed date<br>: Product name, active ingredient<br>: Pharmaceutical form<br>: Marketing authorization holder<br>: Link to notification of a suspected adverse rection<br>: Black triangle symbol-medicine under additional monitoring | : SPC, PIL, EPAR |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 30 | Sweden | HIC | Europe | / | Pharmaceutical facts<br>https://www.lakemedelsverket.se/sv/sok-lakemedelsfakta?activeTab=1 | : Drug name, Strength, pharmaceutical form, active substance, type of medicines (H/V)<br>: Marketing authorization holder | x |
| 31 | Switzerland | HIC | Europe | / | The update lists of authorization of medicinal products with new active ingredient<br>https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/authorisations/new-medicines.html<br>Product information<br>https://www.swissmedicinfo.ch/ | : Name of medicinal product, name of active substance, dose strength and dosage form<br>: Application/ indication<br>: ATC code<br>: Approval date | x |
| 32 | The United Kingdom | HIC | Europe | / | Product<br>https://products.mhra.gov.uk/ | : Download MHRA-SPC, MHRA-PIL and MHRA public assessment report | : MHRA-SPC, MHRA-PIL and MHRA public assessment report |
| 33 | Canada | HIC | North America | / | Drug product database<br>https://health-products.canada.ca/dpd-bdpp/index-eng.jsp | : Status (approve), drug identification number<br>: Company<br>: Product name, class (e.g. human)<br>: Schedule (e.g. prescription)<br>: Active ingredient, strength | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 34 | The United States [a] | HIC | North America | / | FDA approved drug | : Drug name, active ingredients, strength, dosage form | : Medication guide, label, letter and review |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | https://www.accessdata.fda.gov/scripts/cder/daf/ | : Marketing status (e.g. prescription)<br>: Approval date<br>: Submission classification (e.g. type1-new molecular entity)<br>: Review priority status (e.g. standard)<br>: Company | |
| 35 | Barbados | HIC | Caribbean | x | x | x | x |
| 36 | Chile | HIC | Latin America | x | x | x | x |
| 37 | Panama | HIC | Latin America | x | x | x | x |
| 38 | Trinidad and Tobago | HIC | Caribbean | / | Lists of drugs registered (PDF file each year)<br>https://health.gov.tt/services/chemistry-food-and-drugs-division?id=93 | : Tradename and form<br>: Manufacturer<br>: Country of origin | x |
| 39 | Uruguay | HIC | Latin America | x | x | x | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 40 | Australia | HIC | Asia | / | Australian register of therapeutic goods<br>https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg | : Product name, active ingredients<br>: Sponsor name<br>: ARTG (e.g. medicine registered) | : Public ARTG summary and product information |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 41 | Brunei Darussalam | HIC | Asia | x | x | x | x |
| 42 | Hong Kong | HIC | Asia | / | Search drug database<br>https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/search_drug_database.html<br><br>Newly registry medicines<br>https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/home.html | : Product name<br>: Registration number<br>: Certificate holder and address<br>: Legal classification<br>: Sale requirement (e.g. prescription only medicines)<br>: Ingredient<br>: Date of registration | x |
| 43 | Japan [a] | HIC | Asia | / | Prescription drug information<br>https://www.pmda.go.jp/PmdaSearch/iyakuSearch/<br><br>Lists of newly approved drugs<br>(PDF file each year)<br>https://www.pmda.go.jp/english/review-services/reviews/approved-information/drugs/0002.html | : Common name, brand name, manufacturers<br>: Review category<br>: Approval date<br>: Brand name<br>: New approval/ partial change<br>: Active ingredient (underlined: new active ingredient) | : Package insert, RMP material |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 44 | Korea (South) | HIC | Asia | x | x | x | x |
| 45 | New Caledonia | HIC | Asia | x | x | x | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 46 | New Zealand | HIC | Asia | / | Medicine information<br>https://www.medsafe.govt.nz/Medicines/infoSearch.asp | : Active ingredients, trade name, sponsor, registration status (approval) | : Data sheet and consumer medicine information |
| 47 | Singapore | HIC | Asia | / | Register of therapeutic product<br>https://www.hsa.gov.sg/e-services/infosearch | : Product name<br>: Registration number<br>: Registrant | x |
| 48 | Taiwan | HIC | Asia | x | x | x | x |
| 49 | Israel | HIC | Arab | / | Drug registry<br>https://data.health.gov.il/drugs/index.html#!/byDrug | : Active ingredient, dosage form<br>: ATC code<br>: Full registration number<br>: Name of registrar | x |
| 50 | Oman | HIC | Arab | x | x | x | x |
| 51 | Saudi Arabia | HIC | Arab | / | Drug lists<br>https://www.sfda.gov.sa/en/drugs-list | : Scientific name, trade name, strength, dosage form, route of administration, size, package type<br>: Legal status, product control<br>: Distribution site<br>: Shelf life, storage conditions<br>: Manufacturer, marketing company<br>: ATC code, price | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 52 | The United Arab Emirates | HIC | Arab | x | x | x | x |
| 53 | Mauritius | HIC | Africa | x | x | x | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 54 | Albania | UMIC | Europe | / | Drug register (Excel file)<br>http://akbpm.gov.al/ | : Trade name, form/dosage, active ingredient, packing<br>: Registration date, ATC code | x |
| 55 | Armenia | UMIC | Europe | / | Database of registered medicines<br>http://pharm.cals.am/pharm/drug_images/index.php | : Tradename, generic, dosage form, dosage, strength<br>: Manufacturer, country<br>: Registered till<br>: Dispensing by (prescription)<br>: Under control | : Leaflet, SPC |
| 56 | Azerbaijan | UMIC | Europe | / | Search for medicine<br>http://www.pharma.az/ | : Name of the drug, composition, form and trade packaging<br>: Applicant firm/country<br>: Manufacturer/country<br>: Registration card number<br>: Date of issue of registration card<br>: Expiration date of registration | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 57 | Belarus | UMIC | Europe | / | Registered medicine<br>https://www.rceth.by/Refbank | : Tradename, international name<br>: Manufacturer, the applicant<br>: ID number<br>: Registration date, validity date | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | : Original | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | x | x | x | x |
| 59 | Bulgaria | UMIC | Europe | / | Registered medicinal products (search by alphabet) https://www.bda.bg/images/stories/documents/register/Mp.htm | : Tradename, international non-patent names<br>: Manufacturer, country<br>: Active ingredient<br>: ATC code | x |
| 60 | Kazakhstan | UMIC | Europe | x | x | x | x |
| 61 | Montenegro | UMIC | Europe | x | x | x | x |
| 62 | North Macedonia | UMIC | Europe | / | Drug register https://lekovi.zdravstvo.gov.mk/drugsregister/overview | : Latin name, generic name, strength, packing, pharmaceutical form<br>: Manner of issuance<br>: Authorization holder<br>: Date of decision, date of validity, date of renewal<br>: Generic/Originator/Biosimilar drug | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 63 | Russia | UMIC | Europe | x | x | x | x |
| 64 | Serbia | UMIC | Europe | / | Search human medicines https://www.alims.gov.rs/eng/medicinal-products/search-for-human-medicines/?text=Human%20medicines | : Medicine name, INN/common name<br>: Classification, form and packing<br>: MA number, MA date | : SPC, PIL, the text for outer and inner packing |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | : Manufacturer, MAH<br>: ATC code, type of medicine | |
| 65 | Turkey | UMIC | Europe | x | x | x | x |
| 66 | Argentina | UMIC | Latin America | / | National database of medicine<br>http://anmatvademecum.servicios.pami.org.ar/index.html<br><br>https://servicios.pami.org.ar/vademecum/views/consultaPublica/listado.zul | : Certification number, trade name, generic name, pharmaceutical form<br>: Route of administration, presentation, retail price, traceability label | : PIL |
| 67 | Belize | UMIC | Caribbean | x | x | x | x |
| 68 | Brazil | UMIC | Latin America | / | New drugs and indications<br>(line listing of new drugs registered in the last 12 months on website)<br>https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes | : Product name, company, category<br>: Indication<br>: Approval date | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 69 | Colombia | UMIC | Latin America | x | x | x | x |
| 70 | Costa Rica | UMIC | Latin America | x | x | x | x |
| 71 | Cuba | UMIC | Latin America | x | x | x | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 72 | Dominican Republic | UMIC | Latin America | x | x | x | x |
| 73 | Guatemala | UMIC | Latin America | x | x | x | x |
| 74 | Jamaica | UMIC | Caribbean | x | x | x | x |
| 75 | Mexico | UMIC | Latin America | x | x | x | x |
| 76 | Peru | UMIC | Latin America | x | x | x | x |
| 77 | Venezuela, RB | UMIC | Latin America | / | Approved medicines http://www.inhrr.gob.ve/ficha_farma.php | : Download data sheet for approved medicines (active substance, route of administration, pharmacological, indication, dosage, adverse reaction, interaction, contraindication, packaging and label) | : Data sheet for approved medicines |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 78 | China | UMIC | Asia | / | Database for certificate of pharmaceutical products http://english.nmpa.gov.cn/database.html | : Certificate number, certificate classification<br>: Name of product, dosage form, strength, trade name<br>: Name of manufacturer or product-license holder and address | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | : Certificate issue date, this certificate remains valid until (date)<br>: Status of certificate | |
| 79 | Indonesia | UMIC | Asia | / | Check product<br>https://cekbpom.pom.go.id//home/produk/1psjan5ujf2tt0dl5lr76k65t2/01 | : Registration number, date of issue, validity date until<br>: Product name, preparation form, composition, packaging<br>: Registrant, produced by | x |
| 80 | Malaysia | UMIC | Asia | / | Product search<br>https://npra.gov.my/index.php/en/consumers/information/products-search | : Product name, registration number, holder and address, manufacturer and address<br>: Active ingredient, packaging information | : Consumer medication information |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 81 | Thailand [a] | UMIC | Asia | / | Product information<br>https://porta.fda.moph.go.th/fda_search_all/main/search_center_main.aspx | : Marketing authorization number<br>: Approved date, expiration date<br>: Trade name, pharmaceutical dose form<br>: Category by legislation class<br>: ATC code, indication<br>: Name and address licensee, manufacturer | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | : Marketing authorization status (NC, NBC) | |
| 82 | Iran | UMIC | Arab | / | Lists of drugs (line listing) https://www.fda.gov.ir/en/%d8%af%d8%a7%d8%b1%d9%88/%d8%a7%d9%85%d8%a7%d8%b1-%d8%a7%d8%b7%d9%84%d8%a7%d8%b9%d8%a7%d8%aa/%d9%81%d9%87%d8%b1%d8%b3%d8%aa-%d8%b1%d8%b3%d9%85%db%8c-%d8%af%d8%a7%d8%b1%d9%88%db%8c%db%8c-%da%a9%d8%b4%d9%88%d8%b1 | : Generic<br>: Dosage form<br>: Date of approval | x |
| 83 | Iraq | UMIC | Arab | x | x | x | x |
| 84 | Jordan | UMIC | Arab | x | x | x | x |
| 85 | Botswana | UMIC | Africa | x | x | x | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Authorized drug product database** | **URL link** | **Contents** | **Download file of drug information** |
| 86 | Namibia | UMIC | Africa | / | Medicine register https://nmrc.gov.na/medicine-register | : Applicant, registered name, approved name of activities<br>: Dosage form, strength, dose/unit<br>: Registration number<br>: Registration date<br>: Status | x |
| 87 | South Africa | UMIC | Africa | / | Registered health products | : Registration number, registered date | x |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | https://www.sahpra.org.za/registered-health-products/ | : Proprietary name, dosage form, applicant ingredient | |

a-countries with special issues for new drugs subject to conduct post-authorization safety studies

/ (Yes), x (No), Blank (No information)

Link to EMA https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring



## Appendix F-Public accessibility of ADR reports

| No. | Countries | Level of income | Region | Public accessibility of ADR reports |
|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | x |
| 2 | Austria | HIC | Europe | x |
| 3 | Belgium | HIC | Europe | x |
| 4 | Croatia | HIC | Europe | x |
| 5 | Cyprus | HIC | Europe | x |
| 6 | Czech Republic | HIC | Europe | x |
| 7 | Denmark | HIC | Europe | x |

| | | | | |
|---|---|---|---|---|
| 8 | Estonia | HIC | Europe | x |
| 9 | Finland | HIC | Europe | x |
| 10 | France | HIC | Europe | x |
| 11 | Germany | HIC | Europe | x |
| 12 | Greece | HIC | Europe | x |
| 13 | Hungary | HIC | Europe | x |
| 14 | Iceland | HIC | Europe | x |
| 15 | Ireland | HIC | Europe | x |
| 16 | Italy | HIC | Europe | x |
| 17 | Latvia | HIC | Europe | x |
| 18 | Liechtenstein | HIC | Europe | x |
| 19 | Lithuania | HIC | Europe | x |
| 20 | Luxembourg | HIC | Europe | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Public accessibility of ADR reports** |
| 21 | Malta | HIC | Europe | x |
| 22 | The Netherlands | HIC | Europe | / http://databank.lareb.nl/Bijwerkingen |
| 23 | Norway | HIC | Europe | x |
| 24 | Poland | HIC | Europe | x |
| 25 | Portugal | HIC | Europe | x |
| 26 | Romania | HIC | Europe | x |
| 27 | Slovakia | HIC | Europe | x |
| 28 | Slovenia | HIC | Europe | x |
| 29 | Spain | HIC | Europe | x |

| | | | | |
|---|---|---|---|---|
| 30 | Sweden | HIC | Europe | x |
| 31 | Switzerland | HIC | Europe | x |
| 32 | The United Kingdom | HIC | Europe | / https://yellowcard.mhra.gov.uk/iDAP/ |
| 33 | Canada | HIC | North America | / https://cvp-pcv.hc-sc.gc.ca/arq-rei/index-eng.jsp |
| 34 | The United States | HIC | North America | / https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard |
| 35 | Barbados | HIC | Caribbean | x |
| 36 | Chile | HIC | Latin America | x |
| 37 | Panama | HIC | Latin America | x |
| 38 | Trinidad and Tobago | HIC | Caribbean | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Public accessibility of ADR reports** |
| 39 | Uruguay | HIC | Latin America | x |
| 40 | Australia | HIC | Asia | / https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx |
| 41 | Brunei Darussalam | HIC | Asia | x |
| 42 | Hong Kong | HIC | Asia | x |
| 43 | Japan | HIC | Asia | x |
| 44 | Korea (South) | HIC | Asia | x |
| 45 | New Caledonia | HIC | Asia | x |
| 46 | New Zealand | HIC | Asia | / http://www.medsafe.govt.nz/Projects/B1/ADRSearch. Asp |

| | | | | |
|---|---|---|---|---|
| 47 | Singapore | HIC | Asia | / https://www.moh.gov.sg/hpp/all-healthcare-professionals/healthcare-professionals-search |
| 48 | Taiwan | HIC | Asia | x |
| 49 | Israel | HIC | Arab | x |
| 50 | Oman | HIC | Arab | x |
| 51 | Saudi Arabia | HIC | Arab | x |
| 52 | The United Arab Emirates | HIC | Arab | x |
| 53 | Mauritius | HIC | Africa | x |
| 54 | Albania | UMIC | Europe | x |
| 55 | Armenia | UMIC | Europe | x |
| 56 | Azerbaijan | UMIC | Europe | x |
| 57 | Belarus | UMIC | Europe | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Public accessibility of ADR reports** |
| 58 | Bosnia and Herzegovina | UMIC | Europe | x |
| 59 | Bulgaria | UMIC | Europe | x |
| 60 | Kazakhstan | UMIC | Europe | x |
| 61 | Montenegro | UMIC | Europe | x |
| 62 | North Macedonia | UMIC | Europe | x |
| 63 | Russia | UMIC | Europe | x |
| 64 | Serbia | UMIC | Europe | x |
| 65 | Turkey | UMIC | Europe | x |
| 66 | Argentina | UMIC | Latin America | x |
| 67 | Belize | UMIC | Caribbean | x |

| 68 | Brazil | UMIC | Latin America | x |
|---|---|---|---|---|
| 69 | Colombia | UMIC | Latin America | x |
| 70 | Costa Rica | UMIC | Latin America | x |
| 71 | Cuba | UMIC | Latin America | x |
| 72 | Dominican Republic | UMIC | Latin America | x |
| 73 | Guatemala | UMIC | Latin America | x |
| 74 | Jamaica | UMIC | Caribbean | x |
| 75 | Mexico | UMIC | Latin America | x |
| 76 | Peru | UMIC | Latin America | x |
| 77 | Venezuela, RB | UMIC | Latin America | x |
| 78 | China | UMIC | Asia | x |
| 79 | Indonesia | UMIC | Asia | x |
| 80 | Malaysia | UMIC | Asia | x |
| **No.** | **Countries** | **Level of income** | **Region** | **Public accessibility of ADR reports** |
| 81 | Thailand | UMIC | Asia | x |
| 82 | Iran | UMIC | Arab | x |
| 83 | Iraq | UMIC | Arab | x |
| 84 | Jordan | UMIC | Arab | x |
| 85 | Botswana | UMIC | Africa | x |
| 86 | Namibia | UMIC | Africa | x |
| 87 | South Africa | UMIC | Africa | x |

/ (Yes), x (No)

## Appendix G-RMP product coverage scope

| No. | Countries | Level of income | Region | RMP | New chemical entities | New combination | New indication | New dosage form | New route of administration | New strength | New delivery system | New salts | New biologic products |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | | | | | | | | | | |
| 2 | Austria | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 3 | Belgium | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 4 | Croatia | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 5 | Cyprus | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 6 | Czech Republic | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 7 | Denmark | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 8 | Estonia | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 9 | Finland | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 10 | France | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 11 | Germany | HIC | Europe | / | / | x | / | / | / | x | x | x | / |

| 12 | Greece | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | Hungary | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 14 | Iceland | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 15 | Ireland | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 16 | Italy | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 17 | Latvia | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 18 | Liechtenstein | HIC | Europe | | | | | | | | | | |
| 19 | Lithuania | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| **No.** | **Countries** | **Level of income** | **Region** | **RMP** | **New chemical entities** | **New combination** | **New indication** | **New dosage form** | **New route of administration** | **New strength** | **New delivery system** | **New salts** | **New biologic products** |
| 20 | Luxembourg | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 21 | Malta | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 22 | Netherland | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 23 | Norway | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 24 | Poland | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 25 | Portugal | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 26 | Romania | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 27 | Slovakia | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 28 | Slovenia | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 29 | Spain | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 30 | Sweden | HIC | Europe | / | / | x | / | / | / | x | x | x | / |
| 31 | Switzerland | HIC | Europe | / | / | x | / | / | / | x | / | x | / |
| 32 | The United Kingdom | HIC | Europe | / | / | / | / | x | / | x | x | x | / |

| 33 | Canada | HIC | North America | / | / | / | / | / | / | / | x | x | / |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 34 | The United States | HIC | North America | / | / | / | / | / | / | / | / | / | / |
| 35 | Barbados | HIC | Caribbean | | | | | | | | | | |
| 36 | Chile | HIC | Latin America | | | | | | | | | | |
| **No.** | **Countries** | **Level of income** | **Region** | **RMP** | **New chemical entities** | **New combination** | **New indication** | **New dosage form** | **New route of administration** | **New strength** | **New delivery system** | **New salts** | **New biologic products** |
| 37 | Panama | HIC | Latin America | | | | | | | | | | |
| 38 | Trinidad and Tobago | HIC | Caribbean | | | | | | | | | | |
| 39 | Uruguay | HIC | Latin America | | | | | | | | | | |
| 40 | Australia | HIC | Asia | / | / | / | / | x | x | x | x | x | / |
| 41 | Brunei Darussalam | HIC | Asia | | | | | | | | | | |
| 42 | Hong Kong | HIC | Asia | | | | | | | | | | |
| 43 | Japan | HIC | Asia | / | / | / | / | x | / | / | x | x | / |
| 44 | Korea (South) | HIC | Asia | / | | | | | | | | | |
| 45 | New Caledonia | HIC | Asia | | | | | | | | | | |
| 46 | New Zealand | HIC | Asia | / | / | / | / | / | / | x | x | x | / |
| 47 | Singapore | HIC | Asia | / | / | x | x | x | x | x | x | x | / |

| 48 | Taiwan | HIC | Asia | / | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | Israel | HIC | Arab | | | | | | | | | | |
| 50 | Oman | HIC | Arab | / | | | | | | | | | |
| 51 | Saudi Arabia | HIC | Arab | / | | | | | | | | | |
| 52 | The United Arab Emirates | HIC | Arab | / | | | | | | | | | |
| **No.** | **Countries** | **Level of income** | **Region** | **RMP** | **New chemical entities** | **New combination** | **New indication** | **New dosage form** | **New route of administration** | **New strength** | **New delivery system** | **New salts** | **New biologic products** |
| 53 | Mauritius | HIC | Africa | | | | | | | | | | |
| 54 | Albania | UMIC | Europe | | | | | | | | | | |
| 55 | Armenia | UMIC | Europe | | | | | | | | | | |
| 56 | Azerbaijan | UMIC | Europe | | | | | | | | | | |
| 57 | Belarus | UMIC | Europe | | | | | | | | | | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | | | | | | | | | | |
| 59 | Bulgaria | UMIC | Europe | / | | | | | | | | | |
| 60 | Kazakhstan | UMIC | Europe | | | | | | | | | | |
| 61 | Montenegro | UMIC | Europe | | | | | | | | | | |
| 62 | North Macedonia | UMIC | Europe | | | | | | | | | | |
| 63 | Russia | UMIC | Europe | / | | | | | | | | | |
| 64 | Serbia | UMIC | Europe | | | | | | | | | | |
| 65 | Turkey | UMIC | Europe | / | | | | | | | | | |

| 66 | Argentina | UMIC | Latin America | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 67 | Belize | UMIC | Caribbean | | | | | | | | | | |
| 68 | Brazil | UMIC | Latin America | / | | | | | | | | | |
| **No.** | **Countries** | **Level of income** | **Region** | **RMP** | **New chemical entities** | **New combination** | **New indication** | **New dosage form** | **New route of administration** | **New strength** | **New delivery system** | **New salts** | **New biologic products** |
| 69 | Colombia | UMIC | Latin America | | | | | | | | | | |
| 70 | Costa Rica | UMIC | Latin America | | | | | | | | | | |
| 71 | Cuba | UMIC | Latin America | | | | | | | | | | |
| 72 | Dominican Republic | UMIC | Latin America | | | | | | | | | | |
| 73 | Guatemala | UMIC | Latin America | | | | | | | | | | |
| 74 | Jamaica | UMIC | Caribbean | | | | | | | | | | |
| 75 | Mexico | UMIC | Latin America | | | | | | | | | | |
| 76 | Peru | UMIC | Latin America | | | | | | | | | | |
| 77 | Venezuela | UMIC | Latin America | | | | | | | | | | |

| 78 | China | UMIC | Asia | / | / | / | / | / | / | / | x | x | / |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 79 | Indonesia | UMIC | Asia | | | | | | | | | | |
| 80 | Malaysia | UMIC | Asia | / | / | / | / | / | / | / | x | x | / |
| 81 | Thailand | UMIC | Asia | / | x | x | x | x | x | x | x | x | / |
| **No.** | **Countries** | **Level of income** | **Region** | **RMP** | **New chemical entities** | **New combination** | **New indication** | **New dosage form** | **New route of administration** | **New strength** | **New delivery system** | **New salts** | **New biologic products** |
| 82 | Iran | UMIC | Arab | | | | | | | | | | |
| 83 | Iraq | UMIC | Arab | | | | | | | | | | |
| 83 | Jordan | UMIC | Arab | | | | | | | | | | |
| 85 | Botswana | UMIC | Africa | | | | | | | | | | |
| 86 | Namibia | UMIC | Africa | / | | | | | | | | | |
| 87 | South Africa | UMIC | Africa | | | | | | | | | | |

/ (Yes), x (No), Blank (No information)

## Appendix H-Global RMP/Local RMP submission and publication of approved RMP

| No. | Countries | Level of income | Region | Global RMP <u>without</u> local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | | | | |
| 2 | Austria | HIC | Europe | / | | / | /[a] |
| 3 | Belgium | HIC | Europe | / | | / | /[a] |
| 4 | Croatia | HIC | Europe | / | | / | /[a] |
| 5 | Cyprus | HIC | Europe | / | | / | /[a] |
| 6 | Czech Republic | HIC | Europe | / | | / | /[a] |
| 7 | Denmark | HIC | Europe | / | | / | /[a] |
| 8 | Estonia | HIC | Europe | / | | / | /[a] |
| 9 | Finland | HIC | Europe | / | | / | /[a] |
| 10 | France | HIC | Europe | / | | / | /[a] |
| 11 | Germany | HIC | Europe | / | | / | /[a] |
| 12 | Greece | HIC | Europe | / | | / | /[a] |
| 13 | Hungary | HIC | Europe | / | | / | /[a] |
| 14 | Iceland | HIC | Europe | / | | / | /[a] |
| 15 | Ireland | HIC | Europe | / | | / | /[a] |
| 16 | Italy | HIC | Europe | / | | / | /[a] |
| 17 | Latvia | HIC | Europe | / | | / | /[a] |
| 18 | Liechtenstein | HIC | Europe | | | | |
| 19 | Lithuania | HIC | Europe | / | | / | /[a] |

| No. | Countries | Level of income | Region | Global RMP without local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 20 | Luxembourg | HIC | Europe | / | | / | /[a] |
| 21 | Malta | HIC | Europe | / | | / | /[a] |
| 22 | Netherland | HIC | Europe | / | | / | /[a] |
| 23 | Norway | HIC | Europe | / | | / | /[a] |
| 24 | Poland | HIC | Europe | / | | / | /[a] |
| 25 | Portugal | HIC | Europe | / | | / | /[a] |
| 26 | Romania | HIC | Europe | / | | / | /[a] |
| 27 | Slovakia | HIC | Europe | / | | / | /[a] |
| 28 | Slovenia | HIC | Europe | / | | / | /[a] |
| 29 | Spain | HIC | Europe | / | | / | /[a] |
| 30 | Sweden | HIC | Europe | / | | / | /[a] |
| 31 | Switzerland | HIC | Europe | / | | / | / https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/risk-management-rmps/rmp-summaries.html |
| 32 | The United Kingdom | HIC | Europe | / | | / | / |
| 33 | Canada | HIC | North America | / | / | / | x |

| No. | Countries | Level of income | Region | Global RMP without local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 34 | The United States | HIC | North America | / | | / | / https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm |
| 35 | Barbados | HIC | Caribbean | | | | x |
| 36 | Chile | HIC | Latin America | | | | x |
| 37 | Panama | HIC | Latin America | | | | x |
| 38 | Trinidad and Tobago | HIC | Caribbean | | | | x |
| 39 | Uruguay | HIC | Latin America | | | | x |
| 40 | Australia | HIC | Asia | / | / | / | / https://www.tga.gov.au/australian-public-assessment-reports-prescription-medicines-auspars (RMP included in Australian public assessment report) |
| 41 | Brunei Darussalam | HIC | Asia | | | | x |
| 42 | Hong Kong | HIC | Asia | | | | x |

| No. | Countries | Level of income | Region | Global RMP without local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 43 | Japan | HIC | Asia | / | | / | / https://www.pmda.go.jp/english/safety/info-services/drugs/rmp/0001.html |
| 44 | Korea (South) | HIC | Asia | / | | / | x |
| 45 | New Caledonia | HIC | Asia | | | | x |
| 46 | New Zealand | HIC | Asia | / | | / | x |
| 47 | Singapore | HIC | Asia | / | / | / | x |
| 48 | Taiwan | HIC | Asia | / | | | x |
| 49 | Israel | HIC | Arab | | | | x |
| 50 | Oman | HIC | Arab | / | | / | x |
| 51 | Saudi Arabia | HIC | Arab | / | | / | x |
| 52 | The United Arab Emirates | HIC | Arab | / | | / | x |
| 53 | Mauritius | HIC | Africa | | | | x |
| 54 | Albania | UMIC | Europe | | | | x |
| 55 | Armenia | UMIC | Europe | | | | x |
| 56 | Azerbaijan | UMIC | Europe | | | | x |
| 57 | Belarus | UMIC | Europe | | | | x |
| 58 | Bosnia and Herzegovina | UMIC | Europe | | | | x |
| 59 | Bulgaria | UMIC | Europe | / | | / | /[a] |
| 60 | Kazakhstan | UMIC | Europe | | | | x |

| No. | Countries | Level of income | Region | Global RMP without local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 61 | Montenegro | UMIC | Europe | | | | x |
| 62 | North Macedonia | UMIC | Europe | | | | x |
| 63 | Russia | UMIC | Europe | / | | / | x |
| 64 | Serbia | UMIC | Europe | | | | x |
| 65 | Turkey | UMIC | Europe | / | | ICH-E2E | x |
| 66 | Argentina | UMIC | Latin America | | | | x |
| 67 | Belize | UMIC | Caribbean | | | | x |
| 68 | Brazil | UMIC | Latin America | / | | ICH-E2E | x |
| 69 | Colombia | UMIC | Latin America | | | | x |
| 70 | Costa Rica | UMIC | Latin America | | | | x |
| 71 | Cuba | UMIC | Latin America | | | | x |
| 72 | Dominican Republic | UMIC | Latin America | | | | x |
| 73 | Guatemala | UMIC | Latin America | | | | x |
| 74 | Jamaica | UMIC | Caribbean | | | | x |
| 75 | Mexico | UMIC | Latin America | | | | x |
| 76 | Peru | UMIC | Latin America | | | | x |
| 77 | Venezuela | UMIC | Latin America | | | | x |
| 78 | China | UMIC | Asia | / | | / | x |
| 79 | Indonesia | UMIC | Asia | | | | x |
| 80 | Malaysia | UMIC | Asia | / | | / | x |
| 81 | Thailand | UMIC | Asia | / | / | EU, US, Japan | x |

| No. | Countries | Level of income | Region | Global RMP without local RMP | Global RMP and local RMP | EU-RMP format | Publication of approved RMP |
|---|---|---|---|---|---|---|---|
| 82 | Iran | UMIC | Arab | | | | x |
| 83 | Iraq | UMIC | Arab | | | | x |
| 83 | Jordan | UMIC | Arab | | | | x |
| 85 | Botswana | UMIC | Africa | | | | x |
| 86 | Namibia | UMIC | Africa | / | | / | x |
| 87 | South Africa | UMIC | Africa | | | | x |

/ (Yes), x (No), Blank (No information)

a-EU-RMP: https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context (EU-RMP included in European public assessment report)

## Appendix I-Post-authorization safety study

| No. | Countries | Level of income | Region | Risk level |
|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | |
| 2 | Austria | HIC | Europe | x |
| 3 | Belgium | HIC | Europe | x |
| 4 | Croatia | HIC | Europe | x |
| 5 | Cyprus | HIC | Europe | x |
| 6 | Czech Republic | HIC | Europe | x |
| 7 | Denmark | HIC | Europe | x |
| 8 | Estonia | HIC | Europe | x |
| 9 | Finland | HIC | Europe | x |
| 10 | France | HIC | Europe | x |
| 11 | Germany | HIC | Europe | x |
| 12 | Greece | HIC | Europe | x |
| 13 | Hungary | HIC | Europe | x |
| 14 | Iceland | HIC | Europe | x |
| 15 | Ireland | HIC | Europe | x |
| 16 | Italy | HIC | Europe | x |
| 17 | Latvia | HIC | Europe | x |
| 18 | Liechtenstein | HIC | Europe | |
| 19 | Lithuania | HIC | Europe | x |
| 20 | Luxembourg | HIC | Europe | x |
| 21 | Malta | HIC | Europe | x |
| 22 | Netherland | HIC | Europe | x |

| No. | Countries | Level of income | Region | Risk level |
|---|---|---|---|---|
| 23 | Norway | HIC | Europe | x |
| 24 | Poland | HIC | Europe | x |
| 25 | Portugal | HIC | Europe | x |
| 26 | Romania | HIC | Europe | x |
| 27 | Slovakia | HIC | Europe | x |
| 28 | Slovenia | HIC | Europe | x |
| 29 | Spain | HIC | Europe | x |
| 30 | Sweden | HIC | Europe | x |
| 31 | Switzerland | HIC | Europe | x |
| 32 | The United Kingdom | HIC | Europe | x |
| 33 | Canada | HIC | North America | x |
| 34 | The United States | HIC | North America | x |
| 35 | Barbados | HIC | Caribbean | |
| 36 | Chile | HIC | Latin America | |
| 37 | Panama | HIC | Latin America | |
| 38 | Trinidad and Tobago | HIC | Caribbean | |
| 39 | Uruguay | HIC | Latin America | |
| 40 | Australia | HIC | Asia | x |
| 41 | Brunei Darussalam | HIC | Asia | |
| 42 | Hong Kong | HIC | Asia | |
| 43 | Japan | HIC | Asia | x |
| 44 | Korea (South) | HIC | Asia | x |
| 45 | New Caledonia | HIC | Asia | |
| 46 | New Zealand | HIC | Asia | x |

| No. | Countries | Level of income | Region | Risk level |
|---|---|---|---|---|
| 47 | Singapore | HIC | Asia | x |
| 48 | Taiwan | HIC | Asia | x |
| 49 | Israel | HIC | Arab | |
| 50 | Oman | HIC | Arab | |
| 51 | Saudi Arabia | HIC | Arab | |
| 52 | The United Arab Emirates | HIC | Arab | |
| 53 | Mauritius | HIC | Arab | |
| 54 | Albania | UMIC | Europe | |
| 55 | Armenia | UMIC | Europe | |
| 56 | Azerbaijan | UMIC | Europe | |
| 57 | Belarus | UMIC | Europe | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | |
| 59 | Bulgaria | UMIC | Europe | x |
| 60 | Kazakhstan | UMIC | Europe | |
| 61 | Montenegro | UMIC | Europe | |
| 62 | North Macedonia | UMIC | Europe | |
| 63 | Russia | UMIC | Europe | |
| 64 | Serbia | UMIC | Europe | |
| 65 | Turkey | UMIC | Europe | x |
| 66 | Argentina | UMIC | Latin America | |
| 67 | Belize | UMIC | Caribbean | |
| 68 | Brazil | UMIC | Latin America | x |
| 69 | Colombia | UMIC | Latin America | |
| 70 | Costa Rica | UMIC | Latin America | |

| No. | Countries | Level of income | Region | Risk level |
|---|---|---|---|---|
| 71 | Cuba | UMIC | Latin America | |
| 72 | Dominican Republic | UMIC | Latin America | |
| 73 | Guatemala | UMIC | Latin America | |
| 74 | Jamaica | UMIC | Caribbean | |
| 75 | Mexico | UMIC | Latin America | |
| 76 | Peru | UMIC | Latin America | |
| 77 | Venezuela, RB | UMIC | Latin America | |
| 78 | China | UMIC | Asia | x |
| 79 | Indonesia | UMIC | Asia | |
| 80 | Malaysia | UMIC | Asia | |
| 81 | Thailand | UMIC | Asia | / |
| 82 | Iran | UMIC | Arab | |
| 83 | Iraq | UMIC | Arab | |
| 84 | Jordan | UMIC | Arab | |
| 85 | Botswana | UMIC | Africa | |
| 86 | Namibia | UMIC | Africa | |
| 87 | South Africa | UMIC | Africa | |

/ (Yes), x (No), Blank (countries without the requirement for PASS)

## Appendix J-ADR reporting channels and time to reports ADR

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | x | / | / | / | / | x | | | |
| 2 | Austria | HIC | Europe | / | / | / | / | / | x | | 15 days | 90 days |
| 3 | Belgium | HIC | Europe | / | / | x | x | x | x | | 15 days | 90 days |
| 4 | Croatia | HIC | Europe | / | / | x | / | / | / | | 15 days | 90 days |
| 5 | Cyprus | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 6 | Czech Republic | HIC | Europe | x | / | x | x | / | x | | 15 days | 90 days |
| 7 | Denmark | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 8 | Estonia | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 9 | Finland | HIC | Europe | / | / | x | x | x | x | | 15 days | 90 days |
| 10 | France | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 11 | Germany | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 12 | Greece | HIC | Europe | x | / | x | / | x | x | | 15 days | 90 days |
| 13 | Hungary | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 14 | Iceland | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 15 | Ireland | HIC | Europe | / | / | x | x | / | x | | 15 days | 90 days |
| 16 | Italy | HIC | Europe | x | / | x | / | / | x | | 15 days | 90 days |
| 17 | Latvia | HIC | Europe | x | / | / | x | x | x | | 15 days | 90 days |
| 18 | Liechtenstein | HIC | Europe | / | x | x | x | x | x | | | |
| 19 | Lithuania | HIC | Europe | / | / | / | / | / | x | | 15 days | 90 days |

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Luxembourg | HIC | Europe | x | / | / | / | / | x | | 15 days | 90 days |
| 21 | Malta | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 22 | The Netherlands | HIC | Europe | x | / | x | x | x | / | | 15 days | 90 days |
| 23 | Norway | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 24 | Poland | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 25 | Portugal | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 26 | Romania | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 27 | Slovakia | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 28 | Slovenia | HIC | Europe | / | / | / | / | / | x | | 15 days | 90 days |
| 29 | Spain | HIC | Europe | / | / | x | x | x | x | | 15 days | 90 days |
| 30 | Sweden | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 31 | Switzerland | HIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 32 | The United Kingdom | HIC | Europe | / | / | / | x | x | / | | 15 days | 90 days |
| 33 | Canada | HIC | North America | / | / | / | / | / | x | | 15 days | |
| 34 | The United States | HIC | North America | / | / | / | / | / | x | | 15 days | |
| 35 | Barbados | HIC | Caribbean | x | / | x | x | x | x | | | |
| 36 | Chile | HIC | Latin America | / | / | x | / | x | x | | | |

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | Panama | HIC | Latin America | x | x | x | / | / | x | | 5 days | |
| 38 | Trinidad and Tobago | HIC | Caribbean | x | / | x | x | x | x | | | |
| 39 | Uruguay | HIC | Latin America | x | x | x | / | / | x | | | |
| 40 | Australia | HIC | Asia | x | / | / | x | / | x | | 15 days | |
| 41 | Brunei Darussalam | HIC | Asia | / | x | x | x | x | x | 24 hr. | 7 days | 7 days |
| 42 | Hong Kong | HIC | Asia | / | / | x | / | / | x | | 15 days | |
| 43 | Japan | HIC | Asia | / | / | x | / | / | x | 7 days | 15 days | |
| 44 | Korea (South) | HIC | Asia | / | / | x | / | / | x | | 15 days | 15 days |
| 45 | New Caledonia | HIC | Asia | x | x | x | / | / | x | | | |
| 46 | New Zealand | HIC | Asia | / | / | / | / | / | / | | 15 days | 15 days |
| 47 | Singapore | HIC | Asia | / | / | / | / | / | / | | 15 days | |
| 48 | Taiwan | HIC | Asia | x | / | x | / | / | x | 7 days | 15 days | |
| 49 | Israel | HIC | Arab | / | / | / | x | x | x | | | |
| 50 | Oman | HIC | Arab | / | / | x | / | / | / | | 15 days | 15 days |
| 51 | Saudi Arabia | HIC | Arab | / | / | / | / | / | x | | 15 days | 90 days |
| 52 | The United Arab Emirates | HIC | Arab | / | / | x | x | / | x | | 15 days | 90 days |

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 53 | Mauritius | HIC | Africa | / | / | / | / | / | x | | 15 days | |
| 54 | Albania | UMIC | Europe | / | / | x | x | / | x | | | |
| 55 | Armenia | UMIC | Europe | x | / | / | x | x | x | 7 days | 15 days | |
| 56 | Azerbaijan | UMIC | Europe | / | / | / | / | / | x | | | |
| 57 | Belarus | UMIC | Europe | x | / | x | x | x | x | | | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | x | / | x | / | / | x | | | |
| 59 | Bulgaria | UMIC | Europe | x | / | x | x | x | x | | 15 days | 90 days |
| 60 | Kazakhstan | UMIC | Europe | x | / | / | x | / | x | | | |
| 61 | Montenegro | UMIC | Europe | x | / | x | x | x | x | | | |
| 62 | North Macedonia | UMIC | Europe | x | / | x | x | x | x | | | |
| 63 | Russia | UMIC | Europe | x | / | x | x | x | x | 7 days | 15 days | |
| 64 | Serbia | UMIC | Europe | x | / | x | x | x | x | | 15 days | |
| 65 | Turkey | UMIC | Europe | / | / | x | x | x | x | | 15 days | |
| 66 | Argentina | UMIC | Latin America | / | / | / | / | / | x | | 15 days | |
| 67 | Belize | UMIC | Caribbean | x | / | x | x | x | x | | | |
| 68 | Brazil | UMIC | Latin America | x | / | x | x | x | x | 7 days | 15 days | 15 days |

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 69 | Colombia | UMIC | Latin America | / | / | x | x | x | x | | 72 hr. | |
| 70 | Costa Rica | UMIC | Latin America | x | x | / | / | x | x | | 24 hr. | |
| 71 | Cuba | UMIC | Latin America | x | / | / | / | x | x | | 72 hr. | |
| 72 | Dominican Republic | UMIC | Latin America | x | / | / | / | x | x | | | |
| 73 | Guatemala | UMIC | Latin America | / | x | x | x | / | x | | 15 days | |
| 74 | Jamaica | UMIC | Caribbean | / | / | x | x | / | x | | 15 days | 90 days |
| 75 | Mexico | UMIC | Latin America | x | / | x | / | / | x | 7 days | 15 days | 30 days |
| 76 | Peru | UMIC | Latin America | / | x | x | / | / | x | | 24 hr. | |
| 77 | Venezuela, RB | UMIC | Latin America | x | / | x | x | x | x | | | |
| 78 | China | UMIC | Asia | x | / | / | / | x | x | | 15 days | |
| 79 | Indonesia | UMIC | Asia | x | / | x | x | x | x | | 15 days | 30 days |
| 80 | Malaysia | UMIC | Asia | / | / | x | / | / | x | 7 days | 15 days | |
| 81 | Thailand | UMIC | Asia | / | / | x | / | / | x | 24 hr. | 15 days | 60 days |

| No. | Countries | Level of income | Region | Post | Website | Phone | Fax | E-mail | Smart phone application | Time to report fatal | Time to report serious ADR | Time to report non-serious ADR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 82 | Iran | UMIC | Arab | x | / | x | x | x | x | | | |
| 83 | Iraq | UMIC | Arab | / | / | x | x | / | x | 15 days | 30 days | 180 days |
| 84 | Jordan | UMIC | Arab | x | / | x | x | x | x | | 15 days | 90 days |
| 85 | Botswana | UMIC | Africa | / | / | / | / | / | / | | 15 days | 15 days |
| 86 | Namibia | UMIC | Africa | / | / | x | / | / | x | | 15 days | |
| 87 | South Africa | UMIC | Africa | / | / | x | x | / | x | | 15 days | |

/ (Yes), x (No), Blank (No information)

# Appendix K-URL website of ADR reporting

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | / | https://www.salut.ad/RAM/ |
| 2 | Austria | HIC | Europe | / | https://nebenwirkung.basg.gv.at/meldende-person.php |
| 3 | Belgium | HIC | Europe | / | https://www.famhp.be/en/human_use/medicines/medicines/pharmacovigilance/data_collection_evaluation_measures<br>https://famhp-vons.prd.pub.vascloud.be/fr/form/PVH |
| 4 | Croatia | HIC | Europe | / | https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=HR |
| 5 | Cyprus | HIC | Europe | / | https://www.phs.moh.gov.cy/yellowcard/index.jsf |
| 6 | Czech Republic | HIC | Europe | / | http://www.sukl.eu/medicines/phv-4-version-7 |
| 7 | Denmark | HIC | Europe | / | https://laegemiddelstyrelsen.dk/da/bivirkninger/bivirkninger-ved-medicin/meld-en-bivirkning/mennesker/<br>https://blanket.laegemiddelstyrelsen.dk/forms/hcpform/reactions/ |
| 8 | Estonia | HIC | Europe | / | https://www.ravimiamet.ee/en/reporting-requirements-individual-case-safety-reports-icsrs-applicable-marketing-authorisation-0 |
| 9 | Finland | HIC | Europe | / | https://www.fimea.fi/web/en/pharmaceutical_safety_and_information/pharmaceutical_safety/reporting_adverse_reactions |
| 10 | France | HIC | Europe | / | https://ansm.sante.fr/documents/reference/declarer-un-effet-indesirable |
| 11 | Germany | HIC | Europe | / | https://www.bfarm.de/DE/Arzneimittel/Pharmakovigilanz/Risiken-melden/_node.html |
| 12 | Greece | HIC | Europe | / | https://www.eof.gr/web/guest/yellowgeneral |
| 13 | Hungary | HIC | Europe | / | https://ogyei.gov.hu/adverse_drug_reaction_reporting |
| 14 | Iceland | HIC | Europe | / | https://www.serlyfjaskra.is/Aukaverkun/Registration/RegistrationSteps.aspx |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 15 | Ireland | HIC | Europe | / | https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form |
| 16 | Italy | HIC | Europe | / | https://www.aifa.gov.it/web/guest/content/segnalazioni-reazioni-avverse<br>https://www.vigifarmaco.it/report/reports/build/steps/patient |
| 17 | Latvia | HIC | Europe | / | https://www.zva.gov.lv/lv/veselibas-aprupes-specialistiem-un-iestadem/zales/farmakovigilance/zinot-par-blaknem<br>https://www.zva.gov.lv/zvais/pharmvg/ap |
| 18 | Liechtenstein | HIC | Europe | x | |
| 19 | Lithuania | HIC | Europe | / | https://vapris.vvkt.lt/vvkt-web/public/nrvSpecialist |
| 20 | Luxembourg | HIC | Europe | / | https://sante.public.lu/ |
| 21 | Malta | HIC | Europe | / | http://www.medicinesauthority.gov.mt/adrportal<br>http://www.medicinesauthority.gov.mt/form-details?surID=81&cat=3 |
| 22 | The Netherlands | HIC | Europe | / | https://meldformulier.lareb.nl/Forms/reportform?id=a0083ee5-0979-4412-aabb-9589fff484f9 |
| 23 | Norway | HIC | Europe | / | https://legemiddelverket.no/english/pharmacovigilance |
| 24 | Poland | HIC | Europe | / | http://urpl.gov.pl/en/office |
| 25 | Portugal | HIC | Europe | / | https://www.infarmed.pt/web/infarmed/submissaoram |
| 26 | Romania | HIC | Europe | / | https://www.anm.ro/en/medicamente-de-uz-uman/farmacovigilenta/raporteaza-o-reactie-adversa/<br>https://adr.anm.ro/ |
| 27 | Slovakia | HIC | Europe | / | https://www.sukl.sk/hlavna-stranka/slovenska-verzia/bezpecnost-liekov/hlasenie-o-neziaducich-ucinkoch?page_id=536<br>https://portal.sukl.sk/eskadra/ |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 28 | Slovenia | HIC | Europe | / | https://www.jazmp.si/en/human-medicines/pharmacovigilance/reporting-suspected-adverse-drug-reactions/ |
| 29 | Spain | HIC | Europe | / | https://www.notificaram.es/Pages/CCAA.aspx#no-back-button |
| 30 | Sweden | HIC | Europe | / | https://www.lakemedelsverket.se/sv/rapportera-biverkningar/lakemedel |
| 31 | Switzerland | HIC | Europe | / | https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/pharmacovigilance.html https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/pharmacovigilance/elvis.html |
| 32 | The United Kingdom | HIC | Europe | / | https://yellowcard.mhra.gov.uk/yellowcards/reportmediator/ |
| 33 | Canada | HIC | North America | / | https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug.html |
| 34 | The United States | HIC | North America | / | https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=professional.reporting1 |
| 35 | Barbados | HIC | Caribbean | / | https://barbados.seamlessdocs.com/f/Adverse_Drug_Reaction_Reporting_Form https://carpha.org/What-We-Do/CRS/VigiCarib |
| 36 | Chile | HIC | Latin America | / | http://sistemared-ram.ispch.gob.cl/farmacovigilancia/Login.aspx |
| 37 | Panama | HIC | Latin America | x | |
| 38 | Trinidad and Tobago | HIC | Caribbean | / | https://docs.google.com/forms/d/e/1FAIpQLSfCu6PlefCxvw6cXtisA4lCiSILGOKCvGqFDTmw_DSfkDBbyg/viewform https://carpha.org/What-We-Do/CRS/VigiCarib |
| 39 | Uruguay | HIC | Latin America | x | |
| 40 | Australia | HIC | Asia | / | https://aems.tga.gov.au/ https://aems.tga.gov.au/privacy/ |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 41 | Brunei Darussalam | HIC | Asia | x | |
| 42 | Hong Kong | HIC | Asia | / | https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting/adr_report_form_electronic.html |
| 43 | Japan | HIC | Asia | / | https://www.pmda.go.jp/english/ |
| 44 | Korea (South) | HIC | Asia | / | https://www.mfds.go.kr/ |
| 45 | New Caledonia | HIC | Asia | x | |
| 46 | New Zealand | HIC | Asia | / | https://nzphvc.otago.ac.nz/reporting/#how-to-report<br>https://nzphvc.otago.ac.nz/report/ |
| 47 | Singapore | HIC | Asia | / | https://www.hsa.gov.sg/adverse-events<br>https://eservice.hsa.gov.sg/adr/adr/adrOnline.do?action=loadOnlineForm |
| 48 | Taiwan | HIC | Asia | / | https://www.fda.gov.tw/ENG/ |
| 49 | Israel | HIC | Arab | / | https://www.gov.il/en/service/adverse_effects_reports<br>https://sideeffects.health.gov.il/ |
| 50 | Oman | HIC | Arab | / | https://www.moh.gov.om/en/ereporting-pharmacovigilance-department<br>https://www.moh.gov.om/en/-32 |
| 51 | Saudi Arabia | HIC | Arab | / | https://www.sfda.gov.sa/en/pharmacovigilance |
| 52 | The United Arab Emirates | HIC | Arab | / | https://www.mohap.gov.ae/en/services/adverse-drug-reaction-reporting |
| 53 | Mauritius | HIC | Africa | / | https://health.govmu.org/Pages/Departments-Hospitals/National%20Pharmacovigilance%20Committee/How-to-report.aspx<br>https://form.myjotform.com/80387732894571 |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 54 | Albania | UMIC | Europe | / | http://akbpm.gov.al/formulari-raportimi/<br>http://akbpm.gov.al/formular-poteso/ |
| 55 | Armenia | UMIC | Europe | / | http://www.pharm.am/index.php/en/pharmacovigilance-department<br>https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=AM |
| 56 | Azerbaijan | UMIC | Europe | / | http://www.pharma.az/index.php?lang=3&ind=main&id=62 |
| 57 | Belarus | UMIC | Europe | / | https://www.rceth.by/<br>https://www.rceth.by/Reaction/Account/Login.aspx?ReturnUrl=%2fReaction |
| 58 | Bosnia and Herzegovina | UMIC | Europe | / | http://www.almbih.gov.ba/en/vigilance/ |
| 59 | Bulgaria | UMIC | Europe | / | https://www.bda.bg/bg/%D1%84%D0%BE%D1%80%D0%BC%D1%83%D0%BB%D1%8F%D1%80-%D0%B7%D0%B0-%D1%81%D1%8A%D0%BE%D0%B1%D1%89%D0%B0%D0%B2%D0%B0%D0%BD%D0%B5-%D0%BD%D0%B0-%D0%BD%D0%B5%D0%B6%D0%B5%D0%BB%D0%B0%D0%BD%D0%B8-%D0%BB%D0%B5%D0%BA%D0%B0%D1%80%D1%81%D1%82%D0%B2%D0%B5%D0%BD%D0%B8-%D1%80%D0%B5%D0%B0%D0%BA%D1%86%D0%B8%D0%B8-%D0%BE%D1%82-%D0%BC%D0%B5%D0%B4%D0%B8%D1%86%D0%B8%D0%BD%D1%81%D0%BA%D0%B8-%D1%81%D0%BF%D0%B5%D1%86%D0%B8%D0%B0%D0%BB%D0%B8%D1%81%D1%82%D0%B8 |
| 60 | Kazakhstan | UMIC | Europe | / | https://www.ndda.kz/pages/chto-i-kak-soobshchat-o-vyyavlennom-sluchae-podozrevaemogo-pobochnogo-deistviya-ls_1497347849 |
| 61 | Montenegro | UMIC | Europe | / | https://www.calims.me/Portal/faces/dinamickeStrane?_afrLoop=18807859420886731&paramPut=&paramRender=2&paramS=178&_adf.ctrl-state=m7w2388kd_127 |
| 62 | North Macedonia | UMIC | Europe | / | https://lekovi.zdravstvo.gov.mk/pharmacovigilances |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 63 | Russia | UMIC | Europe | / | https://roszdravnadzor.gov.ru/en https://roszdravnadzor.gov.ru/en |
| 64 | Serbia | UMIC | Europe | / | https://www.alims.gov.rs/eng/pharmacovigilance/reporting-of-adverse-drug-reactions/ https://www.alims.gov.rs/latin/prijava-nezeljene-reakcije-na-humani-lek/ |
| 65 | Turkey | UMIC | Europe | / | https://www.titck.gov.tr |
| 66 | Argentina | UMIC | Latin America | / | https://www.argentina.gob.ar/anmat/farmacovigilancia |
| 67 | Belize | UMIC | Caribbean | / | https://www.health.gov.bz/ https://carpha.org/What-We-Do/CRS/VigiCarib |
| 68 | Brazil | UMIC | Latin America | / | http://portal.anvisa.gov.br/ |
| 69 | Colombia | UMIC | Latin America | / | https://www.invima.gov.co/ |
| 70 | Costa Rica | UMIC | Latin America | x | |
| 71 | Cuba | UMIC | Latin America | / | https://www.cecmed.cu/vigilancia |
| 72 | Dominican Republic | UMIC | Latin America | / | https://www.dominicanasolidaria.org/ |
| 73 | Guatemala | UMIC | Latin America | x | |
| 74 | Jamaica | UMIC | Caribbean | / | https://www.moh.gov.jm/divisions-agencies/divisions/standards-and-regulation-division/pharmacovigilance/ https://carpha.org/What-We-Do/CRS/VigiCarib |
| 75 | Mexico | UMIC | Latin America | / | https://www.gob.mx/cofepris/acciones-y-programas/como-notificar-una-sospecha-de-reaccion-adversa?state=published |
| 76 | Peru | UMIC | Latin America | x | |
| 77 | Venezuela, RB | UMIC | Latin America | / | http://www.inhrr.gob.ve/sistema_nacional_farmacovigilancia_ce.php |

| No. | Countries | Level of income | Region | Website | URL website of ADR reporting route |
|---|---|---|---|---|---|
| 78 | China | UMIC | Asia | / | http://english.nmpa.gov.cn/ |
| 79 | Indonesia | UMIC | Asia | / | https://e-meso.pom.go.id/ADR |
| 80 | Malaysia | UMIC | Asia | / | https://npra.gov.my/index.php/en/health-professionals/reporting-adr<br>https://quest3plus.bpfk.gov.my/front-end/adr_web_form_mid.php |
| 81 | Thailand | UMIC | Asia | / | https://privus.fda.moph.go.th/ |
| 82 | Iran | UMIC | Arab | / | http://adr.ttac.ir/ |
| 83 | Iraq | UMIC | Arab | / | https://moh.gov.iq/ |
| 84 | Jordan | UMIC | Arab | / | http://www.jfda.jo/Pages/viewpage.aspx?pageID=173<br>https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=JO |
| 85 | Botswana | UMIC | Africa | / | https://www.bomra.co.bw/index.php/services/patient-safety-monitoring#sppb-tab1-4<br>https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=BW |
| 86 | Namibia | UMIC | Africa | / | https://nmrc.gov.na/tipc1 |
| 87 | South Africa | UMIC | Africa | / | https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA |

/ (Yes), x (No)

## Appendix L-Risk assessment-PSUR submission interval and publication of risk assessment report

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | | x |
| 2 | Austria | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 3 | Belgium | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 4 | Croatia | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | / https://www.halmed.hr/en/O-HALMED-u/Povjerenstva-i-vanjski-suradnici/Povjerenstvo-za-sigurnost-primjene-lijekova/Raspored-sjednica-Sigurnost/ Refer to PRAC recommendation on safety signals and action for marketing authorization holder |
| 5 | Cyprus | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 6 | Czech Republic | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 7 | Denmark | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | / https://laegemiddelstyrelsen.dk/da/bivirkninger/raadet-for-laegemiddelovervaagning/referater-fra-raadet-for-laegemiddelovervaagning-2017-2020/ Discussion on safety signal and recommendation |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 8 | Estonia | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 9 | Finland | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 10 | France | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 11 | Germany | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | / https://www.bfarm.de/EN/Medicinal-products/Pharmacovigilance/Risk-information/Risk-Assessment-Procedures/_node.html Refer to EMA evaluation |
| 12 | Greece | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 13 | Hungary | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 14 | Iceland | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 15 | Ireland | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 16 | Italy | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 17 | Latvia | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 18 | Liechtenstein | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 19 | Lithuania | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 20 | Luxembourg | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 21 | Malta | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 22 | The Netherlands | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 23 | Norway | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 24 | Poland | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 25 | Portugal | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 26 | Romania | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 27 | Slovakia | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 28 | Slovenia | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 29 | Spain | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 30 | Sweden | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 31 | Switzerland | HIC | Europe | 6 monthly for the first 2 years after approval | x |
| 32 | The United Kingdom | HIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | / https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#summary-minutes<br><br>-Discussion on studies that reported potential increased risk<br>-Consider whether the available evidence is adequate and whether the benefit outweigh risk.<br>-Recommendation whether it needs to take regulatory action. |
| 33 | Canada | HIC | North America | 6 monthly for the first 2 years after approval, thereafter annually | / https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews.html<br><br>-Product, potential safety issue, key message, overview, use in Canada<br>-Safety review finding<br>-Conclusion and actions<br>-Additional information, footnote |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 34 | The United States | HIC | North America | 6 monthly for the first 2 years after approval, thereafter annually | / https://www.fda.gov/drugs/drug-safety-and-availability/postmarket-drug-safety-information-patients-and-providers https://www.fda.gov/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations -Product name: Trade (active ingredient) with dosage form -NDA/BLA number (“NME” indicates new molecular entity), approval date -Major indication -Summary of findings from evaluation -Action taken and ongoing surveillance activities |
| 35 | Barbados | HIC | Caribbean | | x |
| 36 | Chile | HIC | Latin America | | x |
| 37 | Panama | HIC | Latin America | | x |
| 38 | Trinidad and Tobago | HIC | Caribbean | | x |
| 39 | Uruguay | HIC | Latin America | 6 monthly for the first 2 years after approval | x |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 40 | Australia | HIC | Asia | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | / https://www.tga.gov.au/acm-meeting-statements Discussion on safety signal from ICSRs, case series articles, meta-analysis, international reports and EU regulatory action taken |
| 41 | Brunei Darussalam | HIC | Asia | 6 monthly for the first two years. Annually for the subsequent 3 years | x |
| 42 | Hong Kong | HIC | Asia | | x |
| 43 | Japan | HIC | Asia | 6 monthly for the first 2 years after approval, and once each year during the remain period of reexamination | x |
| 44 | Korea (South) | HIC | Asia | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 45 | New Caledonia | HIC | Asia | | x |
| 46 | New Zealand | HIC | Asia | 6 monthly for the first 2 years after approval | / https://www.medsafe.govt.nz/profs/MARC/Minutes.asp -Consideration of safety signal by referring to foreign authority agencies such as EU, MHRA and TGA. -Conclusion of benefit-risk balance and recommend regulatory action taken |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 47 | Singapore | HIC | Asia | 6 monthly for the first 2 years after approval, annually for the next 3 years | x |
| 48 | Taiwan | HIC | Asia | 6 monthly for the first 2 years after approval | x |
| 49 | Israel | HIC | Arab | 6 monthly for the first 2 years after approval | x |
| 50 | Oman | HIC | Arab | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 51 | Saudi Arabia | HIC | Arab | 6 monthly for the first 2 years after approval | x |
| 52 | The United Arab Emirates | HIC | Arab | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 53 | Mauritius | HIC | Africa | 6 monthly for the first 2 years after approval | x |
| 54 | Albania | UMIC | Europe | | x |
| 55 | Armenia | UMIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 56 | Azerbaijan | UMIC | Europe | | x |
| 57 | Belarus | UMIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 58 | Bosnia and Herzegovina | UMIC | Europe | | x |
| 59 | Bulgaria | UMIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 60 | Kazakhstan | UMIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 61 | Montenegro | UMIC | Europe | | x |
| 62 | North Macedonia | UMIC | Europe | | x |
| 63 | Russia | UMIC | Europe | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 64 | Serbia | UMIC | Europe | 6 monthly for the first 2 years after approval | x |
| 65 | Turkey | UMIC | Europe | 6 monthly for the first 2 years after approval | x |
| 66 | Argentina | UMIC | Latin America | Annually | x |
| 67 | Belize | UMIC | Caribbean | | x |
| 68 | Brazil | UMIC | Latin America | 6 monthly for the first 2 years after approval | x |
| 69 | Colombia | UMIC | Latin America | 6 monthly for the first 2 years after approval | x |
| 70 | Costa Rica | UMIC | Latin America | | x |
| 71 | Cuba | UMIC | Latin America | Annually the first 3 years, then every 5 years and 10 years | x |
| 72 | Dominican Republic | UMIC | Latin America | | x |
| 73 | Guatemala | UMIC | Latin America | | x |
| 74 | Jamaica | UMIC | Caribbean | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |

| No. | Countries | Level of income | Region | PSUR submission interval | Publication of risk assessment report |
|---|---|---|---|---|---|
| 75 | Mexico | UMIC | Latin America | 6 monthly for the first 2 years after approval, annually the next 3 years, and thereafter every 5years | x |
| 76 | Peru | UMIC | Latin America | | x |
| 77 | Venezuela, RB | UMIC | Latin America | | x |
| 78 | China | UMIC | Asia | 6 monthly for the first 2 years after approval | x |
| 79 | Indonesia | UMIC | Asia | | x |
| 80 | Malaysia | UMIC | Asia | | x |
| 81 | Thailand | UMIC | Asia | 4 monthly for the first 2 years | x |
| 82 | Iran | UMIC | Arab | | x |
| 83 | Iraq | UMIC | Arab | 6 monthly for the first 2 years after approval | x |
| 84 | Jordan | UMIC | Arab | 6 monthly for the first 2 years after approval | x |
| 85 | Botswana | UMIC | Africa | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 86 | Namibia | UMIC | Africa | 6 monthly for the first 2 years after approval, then once a year for the following 2 years and thereafter at 3-yearly interval | x |
| 87 | South Africa | UMIC | Africa | 6 monthly for the first 2 years after approval | x |

/ (Yes), x (No), Blank (No information), EMA-PRAC URL link:

https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management/prac-recommendations-safety-signals

## Appendix M-Risk assessment committee

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | x | | | | |
| 2 | Austria | HIC | Europe | Scientific committee https://www.basg.gv.at/ueber-uns/wissenschaftlicher-ausschuss-des-basg | / Only Chair and Deputy chair | x | 26 | 3 times a year |
| 3 | Belgium | HIC | Europe | Commission for medicinal product for human use https://www.famhp.be/en/commissions/commission_pour_les_medicaments_a_usage_humain_cmh_ | / | Toxicology Pharmacology Clinical medicine Drug analysis Galenic pharmacy Pharmacognosy | 12 | Once a month |
| 4 | Croatia | HIC | Europe | Medicinal products' safety committee https://www.halmed.hr/en/O-HALMED-u/Povjerenstva-i-vanjski-suradnici/Povjerenstvo-za-sigurnost-primjene-lijekova/ | / | Medicines Pharmacy | 23 agency employee and 27 external experts | |
| 5 | Cyprus | HIC | Europe | x | | | | |
| 6 | Czech Republic | HIC | Europe | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 7 | Denmark [a] | HIC | Europe | Pharmacovigilance council<br><br>https://laegemiddelstyrelsen.dk/da/bivirkninger/raadet-for-laegemiddelovervaagning/ | / | Medicines<br>Pharmacy<br>Clinical pharmacology<br>health policy<br>consultant | 11 and<br>1 company<br>1 consumer | 4 times a year |
| 8 | Estonia | HIC | Europe | x | | | | |
| 9 | Finland | HIC | Europe | x | | | | |
| 10 | France | HIC | Europe | Surveillance and pharmacovigilance committee<br><br>https://www.ansm.sante.fr/L-ANSM/Comites-scientifiques-permanents/Comites-scientifiques-permanents/Les-comites-scientifiques-permanents/Comite-Surveillance-et-pharmacovigilance | x | Pharmacovigilance | 15 | 4 times a year |
| 11 | Germany | HIC | Europe | x | | | | |
| 12 | Greece | HIC | Europe | x | | | | |
| 13 | Hungary | HIC | Europe | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 14 | Iceland | HIC | Europe | Pharmaceutical committee<br><br>https://www.ima.is/ima/the_pharmaceutical_committee/ | / | Medicines<br>Pharmacy | 5 | |
| 15 | Ireland | HIC | Europe | Advisory committee human medicines<br><br>http://www.hpra.ie/homepage/about-us/our-structure/advisory-committees | / | Medicines<br>Pharmacy | 10 | 3 times a year |
| 16 | Italy | HIC | Europe | x | | | | |
| 17 | Latvia | HIC | Europe | x | | | | |
| 18 | Liechtenstein | HIC | Europe | x | | | | |
| 19 | Lithuania | HIC | Europe | x | | | | |
| 20 | Luxembourg | HIC | Europe | x | | | | |
| 21 | Malta | HIC | Europe | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 22 | The Netherlands | HIC | Europe | Medicines Evaluation Board<br><br>https://www.cbg-meb.nl/onderwerpen/themas/over-ons-de-organisatie | / | Medicines<br>Clinical pharmacology<br>Drug policy<br>Experience in pharmaceutical manufactures, development and marketing of innovative medicines | 6 | 2 times a year |
| 23 | Norway | HIC | Europe | x | | | | |
| 24 | Poland | HIC | Europe | x | | | | |
| 25 | Portugal | HIC | Europe | x | | | | |
| 26 | Romania | HIC | Europe | x | | | | |
| 27 | Slovakia | HIC | Europe | Commission for medicinal products<br><br>https://www.sukl.sk/hlavna-stranka/slovenska-verzia/o-nas/poradne-organy/komisia-pre-bezpecnost-lieciv/clenovia-komisie-pre-bezpecnost-lieciv?page_id=1860 | / | Medicines<br>Clinical pharmacology<br>Epidemiology<br>Registration of medicines<br>Pharmacovigilance | 16 | 4 times a year |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 28 | Slovenia | HIC | Europe | x | | | | |
| 29 | Spain | HIC | Europe | Committee on the safety of medicines for human use<br>https://www.aemps.gob.es/la-aemps/comites-tecnicos-de-la-aemps/comite-de-seguridad-de-medicamentos-de-uso-humano-csmh/miembros/ | / | Medicines<br>Pharmacy<br>Pharmacovigilance<br>Pharmacoepidemiology | 16 | Once a month |
| 30 | Sweden | HIC | Europe | x | | | | |
| 31 | Switzerland | HIC | Europe | Institute council<br>https://www.swissmedic.ch/swissmedic/de/home/ueber-uns/organisation/institutsrat.html | / | Medicines<br>Cantonal pharmacist<br>Health law | 7 | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 32 | The United Kingdom [b] | HIC | Europe | Pharmacovigilance expert advisory group<br><br>https://www.gov.uk/government/organisations/commission-on-human-medicines/about/membership#pharmacovigilance-eag | / | Medicines<br>Pharmacy<br>Pharmacoepidemiology<br>Pharmacogenetic<br>Clinical pharmacology<br>Clinical toxicology | 12 and 2 Lay representative | Once a month |
| 33 | Canada | HIC | North America | x | | | | |
| 34 | The United States [a] | HIC | North America | Drug safety and risk management advisory committee<br><br>https://www.fda.gov/advisory-committees/drug-safety-and-risk-management-advisory-committee/drug-safety-and-risk-management-advisory-committee-roster | / | Medicines<br>Clinical pharmacology<br>Pharmacoepidemiology<br>Pharmacovigilance<br>Biostatistics<br>Medical toxicology<br>Medicine safety | 11 and<br>1 company and<br>1 consumer | 4 times a year |
| 35 | Barbados | HIC | Caribbean | x | | | | |
| 36 | Chile | HIC | Latin America | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 37 | Panama | HIC | Latin America | x | | | | |
| 38 | Trinidad and Tobago | HIC | Caribbean | x | | | | |
| 39 | Uruguay | HIC | Latin America | x | | | | |
| 40 | Australia | HIC | Asia | Advisory committee on medicines<br>https://www.tga.gov.au/committee/advisory-committee-medicines-acm | / | Medicines<br>Epidemiology<br>Consumer health issues<br>Clinical pharmacology | 20 | Once a month |
| 41 | Brunei Darussalam | HIC | Asia | x | | | | |
| 42 | Hong Kong | HIC | Asia | x | | | | |
| 43 | Japan | HIC | Asia | Science Board<br>https://www.pmda.go.jp/english/rs-sb-std/sb/science-committee/0010.html | / | Medicines<br>Pharmacy | 20 | |
| 44 | Korea (South) | HIC | Asia | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 45 | New Caledonia | HIC | Asia | x | | | | |
| 46 | New Zealand [b] | HIC | Asia | Medicine assessment advisory committee<br>https://www.medsafe.govt.nz/profs/MARC/MARC.asp | / | Epidemiology<br>Medicines<br>Clinical pharmacists<br>Nurse | 10 and<br>1 lay person | 3 times a year |
| 47 | Singapore | HIC | Asia | Product vigilance advisory committee<br>https://www.hsa.gov.sg/about-us/advisory-committees | / | Medicines<br>Pharmacy | 13 | |
| 48 | Taiwan | HIC | Asia | x | | | | |
| 49 | Israel | HIC | Arab | x | | | | |
| 50 | Oman | HIC | Arab | x | | | | |
| 51 | Saudi Arabia | HIC | Arab | x | | | | |
| 52 | The United Arab Emirates | HIC | Arab | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 53 | Mauritius | HIC | Africa | National pharmacovigilance committee<br><br>https://health.govmu.org/Pages/Departments-Hospitals/National%20Pharmacovigilance%20Committee/Composition-of-the-Commitee.aspx | / | Medicines<br>Pharmacy<br>Epidemiology<br>Nurse | 13 | |
| 54 | Albania | UMIC | Europe | x | | | | |
| 55 | Armenia | UMIC | Europe | x | | | | |
| 56 | Azerbaijan | UMIC | Europe | x | | | | |
| 57 | Belarus | UMIC | Europe | x | | | | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | Committee for medicinal products<br><br>http://www.almbih.gov.ba/en/about-us/committees/ | / | Medicines<br>Pharmacy | 16 | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 59 | Bulgaria | UMIC | Europe | Risk safety monitoring committee<br><br>https://www.bda.bg/bg/%D0%B7%D0%B0-%D0%B8%D0%B0%D0%BB/%D0%BA%D0%BE%D0%BC%D0%B8%D1%81%D0%B8%D0%B8-%D0%BA%D1%8A%D0%BC-%D0%B8%D0%B4-%D0%BD%D0%B0-%D0%B8%D0%B0%D0%BB/691-2014-07-17-14-15-21 | / | Medicines<br>Pharmacy<br>Clinical pharmacology<br>Clinical toxicology | 13 | Once a month |
| 60 | Kazakhstan | UMIC | Europe | x | | | | |
| 61 | Montenegro | UMIC | Europe | x | | | | |
| 62 | North Macedonia | UMIC | Europe | x | | | | |
| 63 | Russia | UMIC | Europe | x | | | | |
| 64 | Serbia | UMIC | Europe | x | | | | |
| 65 | Turkey | UMIC | Europe | x | | | | |
| 66 | Argentina | UMIC | Latin America | x | | | | |
| 67 | Belize | UMIC | Caribbean | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 68 | Brazil | UMIC | Latin America | x | | | | |
| 69 | Colombia | UMIC | Latin America | x | | | | |
| 70 | Costa Rica | UMIC | Latin America | x | | | | |
| 71 | Cuba | UMIC | Latin America | x | | | | |
| 72 | Dominican Republic | UMIC | Latin America | x | | | | |
| 73 | Guatemala | UMIC | Latin America | x | | | | |
| 74 | Jamaica | UMIC | Caribbean | x | | | | |
| 75 | Mexico | UMIC | Latin America | x | | | | |
| 76 | Peru | UMIC | Latin America | x | | | | |
| 77 | Venezuela, RB | UMIC | Latin America | x | | | | |
| 78 | China | UMIC | Asia | x | | | | |
| 79 | Indonesia | UMIC | Asia | x | | | | |

| No. | Countries | Level of income | Region | URL | Lists of experts' names | Expert's area | Number of committee member | Frequency of meeting |
|---|---|---|---|---|---|---|---|---|
| 80 | Malaysia | UMIC | Asia | x | | | | |
| 81 | Thailand | UMIC | Asia | x | | | | |
| 82 | Iran | UMIC | Arab | x | | | | |
| 83 | Iraq | UMIC | Arab | x | | | | |
| 84 | Jordan | UMIC | Arab | x | | | | |
| 85 | Botswana | UMIC | Africa | x | | | | |
| 86 | Namibia | UMIC | Africa | x | | | | |
| 87 | South Africa | UMIC | Africa | x | | | | |

a-Denmark and the United States: risk assessment committee consist of regulatory authorities, experts, lay representatives and drug company representatives

b-the United Kingdom and New Zealand: risk assessment committee consist of regulatory authorities, experts and lay representatives

/ (Yes), x (No), Blank (No information)

## Appendix N-Risk communication with URL link

| No. | Countries | Level of income | Region | DHPC Availability | DHPC Post | DHPC E-mail | DHPC Website | Newsletter/ Bulletin Availability | Newsletter/ Bulletin Post | Newsletter/ Bulletin E-mail | Newsletter/ Bulletin Website | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | x | | | x | / | | | / | Alert and press release https://www.salut.ad/alertes-i-comunicats |
| 2 | Austria | HIC | Europe | / | | | / | x | x | x | x | DHPC https://www.basg.gv.at/gesundheitsberufe/sicherheitsinformationen-dhpc |
| 3 | Belgium | HIC | Europe | / | | | / | / | x | x | / | DHPC https://banquededonneesmedicaments.afmps-fagg.be/#/query/human/ News https://www.famhp.be/en/news |
| 4 | Croatia | HIC | Europe | / | | / | / | / | x | / | / | DHPC https://www.halmed.hr/en/Farmakovigilancija/Pisma-zdravstvenim-radnicima/ |
| 5 | Cyprus | HIC | Europe | x | | | x | / | x | x | / | Press release https://www.moh.gov.cy/moh/phs/phs.nsf/pressreleases_el/pressreleases_el?opendocument |
| No. | Countries | | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Czech Republic | HIC | Europe | x | | | x | / | / | / | / | Bulletin https://www.sukl.eu/sukl/publication-activities |
| 7 | Denmark | HIC | Europe | / | | | / | / | x | / | / | DHPC https://laegemiddelstyrelsen.dk/da/bivirkninger/direkte-sikkerhedsinformation/udsendte-meddelelser/ Newsletter https://laegemiddelstyrelsen.dk/da/nyheder/nyhedsbrevet-nyt-fra-laegemiddelstyrelsen/ |
| 8 | Estonia | HIC | Europe | x | | | x | / | x | / | x | |
| 9 | Finland | HIC | Europe | x | | | x | / | x | x | / | New archive https://www.fimea.fi/web/en/about_us/whats_new/news_archive/-/newsarchive/view/category/774874 |
| 10 | France | HIC | Europe | x | | | x | / | x | / | / | News https://ansm.sante.fr/actualites/a-la-une |
| **No.** | **Countries** | | **Region** | **DHPC** | **DHPC** | **DHPC** | **DHPC** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **URL** |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | Germany | HIC | Europe | / | | | / | / | x | x | / | DHPC-Risk information/Rote-Hand Brief and information letter https://www.bfarm.de/EN/Medicinal-products/Pharmacovigilance/Risk-information/Rote-Hand-Briefe-and-Information-Letters/_node.html |
| 12 | Greece | HIC | Europe | x | | | x | / | x | x | / | Announcement to healthcare professionals http://www.eof.gr/web/guest/announcements |
| 13 | Hungary | HIC | Europe | / | | | / | / | x | x | / | DHPC https://ogyei.gov.hu/dhpc_levelek News https://ogyei.gov.hu/hirek |
| 14 | Iceland | HIC | Europe | / | | / | x | / | x | x | / | News https://www.ima.is/ima/publications/news/ |
| **No.** | **Countries** | | **Region** | **DHPC** | **DHPC** | **DHPC** | **DHPC** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **URL** |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | Ireland | HIC | Europe | / | | / | x | / | x | / | / | Newsletter https://www.hpra.ie/homepage/about-us/publications-forms/newsletters |
| 16 | Italy | HIC | Europe | x | | | x | / | x | / | / | Press release https://www.aifa.gov.it/comunicati-stampa |
| 17 | Latvia | HIC | Europe | / | | / | x | / | / | / | / | News https://www.zva.gov.lv/lv/sakums |
| 18 | Liechtenstein | HIC | Europe | x | | | x | x | | | x | |
| 19 | Lithuania | HIC | Europe | / | | | / | / | x | x | / | Letter to healthcare professionals https://www.vvkt.lt/index.php?3139344720 News https://www.vvkt.lt/ |
| 20 | Luxembourg | HIC | Europe | x | | | x | x | | | x | |
| **No.** | **Countries** | | **Region** | **DHPC** | **DHPC** | **DHPC** | **DHPC** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **URL** |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Malta | HIC | Europe | / | | | / | / | x | / | / | DHPC http://www.medicinesauthority.gov.mt/dhpc New archive http://www.medicinesauthority.gov.mt/news-archive?id=F3 |
| 22 | The Netherlands | HIC | Europe | / | | / | x | / | x | / | / | News https://www.cbg-meb.nl/actueel/nieuws?trefwoord=&startdatum=&einddatum=&onderdeel=Medicijninformatie |
| 23 | Norway | HIC | Europe | / | | / | / | / | x | / | / | DHPC https://legemiddelverket.no/bivirkninger-og-sikkerhet/kjere-helsepersonell-brev-sikkerhetsinformasjon-for-helsepersonell News https://legemiddelverket.no/ |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 24 | Poland | HIC | Europe | x | | | x | x | | | x | |
| 25 | Portugal | HIC | Europe | x | | | x | / | x | / | / | News https://www.infarmed.pt/# |
| 26 | Romania | HIC | Europe | / | | / | / | / | x | x | / | DHPC https://www.anm.ro/medicamente-de-uz-uman/farmacovigilenta/comunicari-directe-catre-profesionistii-din-domeniul-sanatatii/ Press release https://www.anm.ro/agentie/comunicate-de-presa/ |
| 27 | Slovakia | HIC | Europe | / | | | / | / | x | x | / | DHPC https://www.sukl.sk/hlavna-stranka/slovenska-verzia/bezpecnost-liekov/oznamy-drzitelov-dhpc?page_id=2155 News https://www.sukl.sk/hlavna-stranka/slovenska-verzia/bezpecnost-liekov/aktuality?page_id=218 |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 28 | Slovenia | HIC | Europe | / | | | / | / | | | / | DHPC https://www.jazmp.si/humana-zdravila/farmakovigilanca/obvestila-za-zdravstvene-delavce/neposredna-obvestila-za-zdravstvene-delavce/ Press release https://www.jazmp.si/arhiv-obvestil/ |
| 29 | Spain | HIC | Europe | / | | | / | / | x | / | / | DHPC https://www.aemps.gob.es/acciones-informativas/boletines-de-la-aemps/boletin-mensual-de-la-aemps-sobre-medicamentos-de-uso-humano/ Bulletin https://www.aemps.gob.es/acciones-informativas/boletines-de-la-aemps/boletin-mensual-de-la-aemps-sobre-medicamentos-de-uso-humano/ |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 30 | Sweden | HIC | Europe | / | | | / | / | / | / | / | DHPC and News https://www.lakemedelsverket.se/sv/saker-anvandning/sakerhetsinformation/lakemedel-for-manniska#hmainbody4 |
| 31 | Switzerland | HIC | Europe | / | | | / | / | x | / | / | DHPC https://www.swissmedic.ch/swissmedic/de/home/humanarzneimittel/marktueberwachung/health-professional-communication--hpc-.html News https://www.swissmedic.ch/swissmedic/de/home/news/updates.html |
| 32 | The United Kingdom | HIC | Europe | / | | | / | / | x | / | / | DHPC https://www.gov.uk/drug-safety-update Drug safety update https://www.gov.uk/drug-safety-update |
| No. | Countries | | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/Bulletin | Newsletter/ Bulletin | URL |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | Canada | HIC | North America | / | | | / | / | | / | / | Health product infoWatch and DHPC https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/published-newsletters.html |
| 34 | The United States | HIC | North America | / | | | / | / | | / | / | Drug safety communication and DHPC https://www.fda.gov/drugs/drug-safety-and-availability/drug-safety-communications |
| 35 | Barbados | HIC | Caribbean | x | | | x | x | | | x | |
| 36 | Chile | HIC | Latin America | x | | | x | / | | | / | News http://www.ispch.cl/prensa |
| 37 | Panama | HIC | Latin America | x | | | x | / | | | / | Medication safety note http://www.minsa.gob.pa/informacion-salud/alertas-y-comunicados |
| 38 | Trinidad and Tobago | HIC | Caribbean | x | | | x | / | | | / | News and press release https://health.gov.tt/media |
| 39 | Uruguay | HIC | Latin America | x | | | x | x | | | x | |
| **No.** | **Countries** | | **Region** | **DHPC** | **DHPC** | **DHPC** | **DHPC** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **Newsletter/ Bulletin** | **URL** |

| | | Level of income | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 40 | Australia | HIC | Asia | x | | | x | / | | / | / | Medicines safety update https://www.tga.gov.au/publication/medicines-safety-update |
| 41 | Brunei Darussalam | HIC | Asia | x | | | x | / | | | / | News http://www.moh.gov.bn/SitePages/Latest%20News.aspx |
| 42 | Hong Kong | HIC | Asia | x | | | x | / | | | / | Safety alert and products recalls https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/safety_alerts_and_medical_recalls/index.html |
| 43 | Japan | HIC | Asia | / | | | / | / | | | / | DHPC https://www.pmda.go.jp/english/safety/info-services/drugs/esc-rsc/0001.html MHLW pharmaceutical and medical devices safety information every month (new drugs subject to EPPV) https://www.pmda.go.jp/english/safety/info-services/drugs/medical-safety-information/0002.html |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 44 | Korea (South) | HIC | Asia | / | | | / | / | | | / | DHPC https://nedrug.mfds.go.kr/pbp/CCBAC01 Press release https://www.mfds.go.kr/brd/m_99/list.do |
| 45 | New Caledonia | HIC | Asia | x | | | x | x | | | x | |
| 46 | New Zealand | HIC | Asia | / | | | / | / | | / | / | DHPC https://www.medsafe.govt.nz/safety/DHCPLetters.asp Medsafe safety communication https://www.medsafe.govt.nz/safety/SafetyCommunications.asp |
| 47 | Singapore | HIC | Asia | / | | | / | / | | | / | DHPC https://www.hsa.gov.sg/announcements?contenttype=Press%20Releases Adverse drug reaction news bulletin https://www.hsa.gov.sg/announcements?contenttype=Press%20Releases |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 48 | Taiwan | HIC | Asia | x | | | x | / | | | / | News https://www.fda.gov.tw/ENG/index.aspx#arrow-up-a |
| 49 | Israel | HIC | Arab | x | | | x | / | | | / | Safety warning https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/Pages/default.aspx |
| 50 | Oman | HIC | Arab | x | | | x | / | | | / | Pharmaceutical newsletter https://www.moh.gov.om/en/web/dgpadc/-8 |
| 51 | Saudi Arabia | HIC | Arab | x | | | x | / | | | / | Warning https://www.sfda.gov.sa/en/warnings?keys=&date%5Bmin%5D=&date%5Bmax%5D=&tags=2&page=0 |
| 52 | The United Arab Emirates | HIC | Arab | x | | | x | x | | | x | |
| 53 | Mauritius | HIC | Africa | x | | | x | x | | | x | |
| 54 | Albania | UMIC | Europe | x | | | x | / | | | / | News http://akbpm.gov.al/sektori-i-farmakovigjilences/ |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 55 | Armenia | UMIC | Europe | / | | | / | / | | | / | DHPC http://www.pharm.am/index.php/en/dear-healthcare-professional-letter Drug and Medicine information Bulletin http://www.pharm.am/index.php/en/dm?limitstart=0 |
| 56 | Azerbaijan | UMIC | Europe | / | | | / | / | | | / | DHPC http://www.pharma.az/index.php?lang=3&ind=main&id=73 News http://www.pharma.az/ |
| 57 | Belarus | UMIC | Europe | x | | | x | / | | | / | New safety of medicinal preparation https://www.rceth.by/en/Safety/DrugSafety |
| 58 | Bosnia and Herzegovina | UMIC | Europe | x | | | x | / | | | / | News http://www.almbih.gov.ba/en/news/ |
| 59 | Bulgaria | UMIC | Europe | x | | | x | / | / | | / | Important information https://www.bda.bg/bg/%D0%B2%D0%B0%D0%B6%D0%BD%D0%B0-%D0%B8%D0%BD%D1%84%D0%BE%D1%80%D0%BC%D0%B0%D1%86%D0%B8%D1%8F |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 60 | Kazakhstan | UMIC | Europe | x | | | x | / | | | / | Newsletter https://www.ndda.kz/category/informacionnye_pisma |
| 61 | Montenegro | UMIC | Europe | / | | | / | / | | | / | DHPC https://www.calims.me/Portal/faces/dinamickeStrane?_afrLoop=22623279933250533&paramPut=+%3E+Pharmacovigilance+%3E+DHPC+-+Direct+Healthcare+Professional+Communication&paramRender=2&paramS=56&_adf.ctrl-state=9jseuor5c_255<br>Newsletter https://www.calims.me/Portal/faces/dinamickeStrane?_adf.ctrl-state=m7w2388kd_127 |
| 62 | North Macedonia | UMIC | Europe | x | | | x | x | | | x | |
| 63 | Russia | UMIC | Europe | x | | | x | / | | | / | Newsletter https://roszdravnadzor.gov.ru/drugs/monitpringlp |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 64 | Serbia | UMIC | Europe | x | | | x | x | | | x | |
| 65 | Turkey | UMIC | Europe | x | | | x | x | | | x | |
| 66 | Argentina | UMIC | Latin America | x | | | x | / | | | / | Alert and withdraw https://www.argentina.gob.ar/anmat/alertas |
| 67 | Belize | UMIC | Caribbean | x | | | x | x | | | x | |
| 68 | Brazil | UMIC | Latin America | x | | | x | / | | | / | Medicine alerts http://antigo.anvisa.gov.br/alertas/-/buscar?p_p_id=anvisabuscaavancada_WAR_anvisabuscaavancadaportlet&keywords=&dataInicial=&dataFinal=&categoryIds=34506 |
| 69 | Colombia | UMIC | Latin America | x | | | x | / | | | / | High alert for medicines and biological products https://app.invima.gov.co/alertas/medicamentos-productos-biologicos |
| 70 | Costa Rica | UMIC | Latin America | x | | | x | x | | | x | |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 71 | Cuba | UMIC | Latin America | x | | | x | / | | | / | Bulletin informative note https://www.cecmed.cu/vigilancia/notas-informativas |
| 72 | Dominican Republic | UMIC | Latin America | x | | | x | x | | | x | |
| 73 | Guatemala | UMIC | Latin America | x | | | x | x | | | x | |
| 74 | Jamaica | UMIC | Caribbean | x | | | x | x | | | x | |
| 75 | Mexico | UMIC | Latin America | x | | | x | x | | | x | |
| 76 | Peru | UMIC | Latin America | x | | | x | / | | | / | Risk communication https://www.digemid.minsa.gob.pe/Main.asp?Seccion=953 Alert and safety sign https://www.digemid.minsa.gob.pe/Main.asp?Seccion=371&SeccionCategoria=3 |
| 77 | Venezuela | UMIC | Latin America | x | | | x | x | | | x | |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 78 | China | UMIC | Asia | x | | | x | / | | | / | Newsletter http://english.nmpa.gov.cn/newsletter.html |
| 79 | Indonesia | UMIC | Asia | x | | | x | / | | | / | Risk communication https://e-meso.pom.go.id/ |
| 80 | Malaysia | UMIC | Asia | x | | | x | / | | | / | Bulletin https://npra.gov.my/index.php/en/health-professionals/newsletter-madrac-bulletin.html |
| 81 | Thailand | UMIC | Asia | / | | | / | / | | | / | DHPC http://hpvc.fda.moph.go.th/AEINFO/NewsPublishList.aspx?PID=10019 HPVC safety news http://hpvc.fda.moph.go.th/AEINFO/NewsPublishList.aspx?PID=10017 Newsletter http://hpvc.fda.moph.go.th/AEINFO/NewsPublishList.aspx?PID=10037 |
| 82 | Iran | UMIC | Arab | x | | | x | x | | | x | |
| 83 | Iraq | UMIC | Arab | x | | | x | x | | | x | |
| 84 | Jordan | UMIC | Arab | x | | | x | x | | | x | |

| No. | Countries | Level of income | Region | DHPC | DHPC | DHPC | DHPC | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | Newsletter/ Bulletin | URL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Availability | Post | E-mail | Website | Availability | Post | E-mail | Website | |
| 85 | Botswana | UMIC | Africa | x | | | x | / | | | / | Press release https://www.bomra.co.bw/index.php/bomra-downloads/publications/category/32-press-releases |
| 86 | Namibia | UMIC | Africa | x | | | x | x | | | x | |
| 87 | South Africa | UMIC | Africa | / | | | / | / | | | / | DHPC https://www.sahpra.org.za/safety-information-and-updates/ Medicine safety alert https://www.sahpra.org.za/safety-information-and-updates/ |

/ (Yes), x (No), Blank (No information)

## Appendix O-PV inspection

| No. | Countries | Level of income | Region | PV inspection | URL |
|---|---|---|---|---|---|
| 1 | Andorra | HIC | Europe | | |
| 2 | Austria | HIC | Europe | / | https://www.basg.gv.at/fuer-unternehmen/pharmakovigilanz/pharmakovigilanz-inspektion |
| 3 | Belgium | HIC | Europe | / | https://www.famhp.be/en/human_use/medicines/medicines/pharmacovigilance/inspections_QPPV |
| 4 | Croatia | HIC | Europe | / | mention in PV guideline |
| 5 | Cyprus | HIC | Europe | / | mention in PV guideline |
| 6 | Czech Republic | HIC | Europe | / | mention in PV guideline |
| 7 | Denmark | HIC | Europe | / | mention in PV guideline |
| 8 | Estonia | HIC | Europe | / | mention in PV guideline |
| 9 | Finland | HIC | Europe | / | https://www.fimea.fi/web/en/supervision/pharmacovigilance/pharmacovigilance-inspections |
| 10 | France | HIC | Europe | / | mention in PV guideline |
| 11 | Germany | HIC | Europe | / | mention in PV guideline |
| 12 | Greece | HIC | Europe | / | mention in PV guideline |
| 13 | Hungary | HIC | Europe | / | mention in PV guideline |
| 14 | Iceland | HIC | Europe | / | mention in PV guideline |
| 15 | Ireland | HIC | Europe | / | http://www.hpra.ie/homepage/medicines/regulatory-information/pharmacovigilance-and-post-authorisation-safety/pharmacovigilance-inspections |
| 16 | Italy | HIC | Europe | / | mention in PV guideline |
| 17 | Latvia | HIC | Europe | / | mention in PV guideline |
| 18 | Liechtenstein | HIC | Europe | | |
| 19 | Lithuania | HIC | Europe | / | https://www.vvkt.lt/index.php?3539289990 |

| No. | Countries | Level of income | Region | PV inspection | URL |
|---|---|---|---|---|---|
| 20 | Luxembourg | HIC | Europe | / | mention in PV guideline |
| 21 | Malta | HIC | Europe | / | http://www.medicinesauthority.gov.mt/goodvigilancepractice |
| 22 | Netherland | HIC | Europe | / | mention in PV guideline |
| 23 | Norway | HIC | Europe | / | mention in PV guideline |
| 24 | Poland | HIC | Europe | / | http://urpl.gov.pl/en/office/clinical-trials-inspection-and-phv/pharmacovigilance-inspection-medicinal-products-human-use |
| 25 | Portugal | HIC | Europe | / | mention in PV guideline |
| 26 | Romania | HIC | Europe | / | mention in PV guideline |
| 27 | Slovakia | HIC | Europe | / | mention in PV guideline |
| 28 | Slovenia | HIC | Europe | / | mention in PV guideline |
| 29 | Spain | HIC | Europe | / | mention in PV guideline |
| 30 | Sweden | HIC | Europe | / | mention in PV guideline |
| 31 | Switzerland | HIC | Europe | | |
| 32 | United Kingdom | HIC | Europe | / | https://www.gov.uk/government/statistics/pharmacovigilance-inspection-metrics-2009-to-present https://www.gov.uk/guidance/good-pharmacovigilance-practice-gpvp#types-of-inspection |
| 33 | Canada | HIC | North America | / | https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/inspection-strategy-pharmacovigilance-drugs-0041.html |
| 34 | The United States | HIC | North America | / | https://www.fda.gov/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations |
| 35 | Barbados | HIC | Caribbean | | |
| 36 | Chile | HIC | Latin America | | |
| 37 | Panama | HIC | Latin America | | |
| 38 | Trinidad and Tobago | HIC | Caribbean | | |

| No. | Countries | Level of income | Region | PV inspection | URL |
|---|---|---|---|---|---|
| 39 | Uruguay | HIC | Latin America | | |
| 40 | Australia | HIC | Asia | / | https://www.tga.gov.au/pharmacovigilance-inspection-program |
| 41 | Brunei Darussalam | HIC | Asia | | |
| 42 | Hong Kong | HIC | Asia | | |
| 43 | Japan | HIC | Asia | / | https://www.pmda.go.jp/english/ |
| 44 | Korea (South) | HIC | Asia | | |
| 45 | New Caledonia | HIC | Asia | | |
| 46 | New Zealand | HIC | Asia | | |
| 47 | Singapore | HIC | Asia | | |
| 48 | Taiwan | HIC | Asia | | |
| 49 | Israel | HIC | Arab | | |
| 50 | Oman | HIC | Arab | / | mention in PV guideline |
| 51 | Saudi Arabia | HIC | Arab | / | mention in PV guideline |
| 52 | The United Arab Emirates | HIC | Arab | | |
| 53 | Mauritius | HIC | Arab | | |
| 54 | Albania | UMIC | Europe | | |
| 55 | Armenia | UMIC | Europe | | |
| 56 | Azerbaijan | UMIC | Europe | | |
| 57 | Belarus | UMIC | Europe | | |
| 58 | Bosnia and Herzegovina | UMIC | Europe | | |
| 59 | Bulgaria | UMIC | Europe | / | mention in PV guideline |
| 60 | Kazakhstan | UMIC | Europe | | |

| No. | Countries | Level of income | Region | PV inspection | URL |
|---|---|---|---|---|---|
| 61 | Montenegro | UMIC | Europe | | |
| 62 | North Macedonia | UMIC | Europe | | |
| 63 | Russia | UMIC | Europe | | |
| 64 | Serbia | UMIC | Europe | | |
| 65 | Turkey | UMIC | Europe | | |
| 66 | Argentina | UMIC | Latin America | | |
| 67 | Belize | UMIC | Caribbean | | |
| 68 | Brazil | UMIC | Latin America | / | http://antigo.anvisa.gov.br/ |
| 69 | Colombia | UMIC | Latin America | / | https://www.invima.gov.co/es/web/guest/biologicos-y-de-sintesis-quimica |
| 70 | Costa Rica | UMIC | Latin America | | |
| 71 | Cuba | UMIC | Latin America | / | https://www.cecmed.cu/vigilancia/farmacovigilancia/industria |
| 72 | Dominican Republic | UMIC | Latin America | | |
| 73 | Guatemala | UMIC | Latin America | | |
| 74 | Jamaica | UMIC | Caribbean | | |
| 75 | Mexico | UMIC | Latin America | | |
| 76 | Peru | UMIC | Latin America | | |
| 77 | Venezuela, RB | UMIC | Latin America | | |
| 78 | China | UMIC | Asia | | |
| 79 | Indonesia | UMIC | Asia | | |
| 80 | Malaysia | UMIC | Asia | | |
| 81 | Thailand | UMIC | Asia | | |
| 82 | Iran | UMIC | Arab | | |
| 83 | Iraq | UMIC | Arab | | |

| No. | Countries | Level of income | Region | PV inspection | URL |
|---|---|---|---|---|---|
| 84 | Jordan | UMIC | Arab | / | http://www.jfda.jo/Pages/viewpage.aspx?pageID=385 |
| 85 | Botswana | UMIC | Africa | | |
| 86 | Namibia | UMIC | Africa | | |
| 87 | South Africa | UMIC | Africa | | |

/ (Yes), x (No), Blank (No information)

## Appendix P-Assessment of pharmacovigilance system of new drugs in Thailand following IPAT indicators and WHO indicators

| Core structure indicators | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| The existence of pharmacovigilance center | √ | √ | √ | √ |
| Pharmacovigilance center has a clear structure, responsibilities and roles | √ | √ | x | |
| The existence of policy or legislation for pharmacovigilance | √ | √ | √ | √ |
| The existence of specific legal for pharmacovigilance | √ | √ | x | |
| The existence of a medicine regulatory agency | x | | √ | √ |
| The existence of human resources | √ | √ | √ | √ |
| The existence of financial provision | √ | √ | √ | √ |
| The existence of ADR reporting form | x | | √ | √ |
| The existence of ADR bulletin | √ | √ | √ | √ |
| The existence of advisory committee | √ | √ | √ | √ |
| The procedure in place for collecting, analyzing and recording of ADR reports | x | | √ | √ |
| The national pharmacovigilance curriculum for the health care professionals | x | | √ | √ |
| The drug information service center which answers on ADRs and drug safety questions | √ | √ | x | |
| The existence of updated pharmacovigilance guidelines within the previous five years | √ | √ | x | |
| The existence of standard operating procedures (SOPs) of medicine use for patient safety | √ | √ | x | |
| The existence of communication technology to provision of drug information and access to safety reporting | √ | √ | x | |

| **Complementary structure indicators** | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| The national pharmacovigilance center participates as the full or the associate member of the WHO collaborating center for international drug monitoring | √ | √ | x | |
| Legislation requires drug companies to mandatorily report all serious ADR to the national pharmacovigilance center | √ | √ | x | |
| Legislation requires drug companies to conduct post-marketing surveillance | √ | √ | x | |
| The existence of requirements commanding drug companies to submit periodic safety update reports | x | | √ | √ |
| The existence of the computers for pharmacovigilance activities | x | | √ | √ |
| The existence of information sources on prescription of drugs and consumptions | x | | √ | √ |
| The existence of communication facilities in the national pharmacovigilance center | x | | √ | √ |
| The existence of additional references or the library for drug safety data | x | | √ | √ |
| The existence of the computerized ADR report system | x | | √ | √ |
| The existence of the program for monitoring the quality of medicinal products | x | | √ | √ |
| The existence of the essential drugs list | x | | √ | √ |
| The existence of pharmacovigilance data when preparing the major standard treatment guideline | x | | √ | √ |
| The national pharmacovigilance center provides training sessions for public and healthcare professionals | x | | √ | √ |
| The existence of web-based pharmacovigilance training instruments for public and healthcare professionals | x | | √ | x |

| Core process indicators | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| Strategy or platform for collaboration of pharmacovigilance activities across all stakeholders | √ | √ | x | |
| The system has the collation of drugs safety data from all sources to the database at the national pharmacovigilance center | √ | √ | x | |
| The existence of the database for pharmacovigilance activities | √ | √ | x | |
| The existence of the suspected ADRs reporting form | √ | √ | x | |
| The existence of the suspected product quality issues reporting form | √ | x | x | |
| The existence of the suspected medication errors reporting form | √ | x | x | |
| The existence of the suspected treatment failure reporting form | √ | x | x | |
| The number of ADR reports obtained in the previous year | √ | √ | √ | √ |
| The number of active surveillances conducted in the previous five years | √ | √ | √ | √ |
| Percentage of the patients who have adverse drug events in public health programs in the previous year | √ | | x | |
| Percentage of the patients who receive new treatment due to ADRs in public health program in the previous year | √ | | x | |
| The number of current reports in the local database or regional or national | x | | √ | √ |
| A percentage of an annual reports acknowledged or feedback | x | | √ | |
| A percentage of the reports aim to causality assessment in the previous year | x | | √ | |
| A percentage of the annual reports completed and submitted to WHO database | x | | √ | |
| A percentage of the therapeutic ineffectiveness report obtained in the last year | x | | √ | |
| A percentage of the medication errors report obtained in the last year | x | | √ | |
| A percentage of the pharmaceutical manufactures have a pharmacovigilance system | x | | √ | |

| Complementary process indicators | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| Percentage of the main reference materials existing in the national pharmacovigilance center | √ | | x | |
| Percentage of the main pharmacovigilance topics presented in the training courses | √ | | √ | |
| The number of healthcare professionals trained on pharmacovigilance and drug safety in the previous year | √ | | √ | |
| The number of drug use reviews processed in the previous year | √ | | x | |
| Medicinal products quality was surveyed in the previous five year | √ | | x | |
| The quantification of incidence of medication errors in the previous year | √ | | x | |
| Percentage of patients who have severe unexpected adverse events in public health programs in the previous year | √ | | x | |
| Percentage of hospitals which submit more than 10 reports to the national pharmacovigilance center | x | | √ | |
| Percentage of the ADR reports sent in the last year by the various stakeholders including physicians, dentists, pharmacists, nurses, general public and manufactures | x | | √ | |
| The total number of ADR reports per million population per year | x | | √ | |
| The average number of ADR reports per number of health professionals per year including physicians, dentists, pharmacists and nurses | x | | √ | |
| Percentage of healthcare professionals understand and aware of ADRs per hospital | x | | √ | |
| Percentage of the patients who leave a hospital aware of ADR | x | | √ | |
| The total number of specific medicinal products reporting per volume of sales from the pharmaceutical manufactures | x | | √ | |

| **Complementary process indicators** | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| The number of registered medicinal products with the risk management plan in the pharmaceutical manufactures | x | | √ | |
| Percentage of pharmaceutical manufactures who submit periodic safety update reports to the drug regulatory agency | x | | √ | |
| Number of medicinal products voluntarily withdrawn by pharmaceutical manufactures due to safety concerns in the last year | x | | √ | |
| Number of ADR reports from individual pharmaceutical manufactures received by the national pharmacovigilance center in the last year | x | | √ | |
| **Core outcome indicators** | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
| Number of regulatory actions | x | | √ | x |
| Number of signals identified in the last 5 years | x | | √ | x |
| Number of drugs related hospital admissions per 1000 admissions | x | | √ | |
| Number of drugs related deaths per 1000 persons per year | x | | √ | |
| Number of drugs related deaths per 100,000 persons in the population | x | | √ | |
| The average cost (US$) of treatment of drugs related sickness | x | | √ | |
| The average period of drugs related expansion of hospital stays | x | | √ | |
| The average cost (US$) of medicine-related hospitalization | x | | √ | |
| The average time lag between detection of signal of a suspected ADR or important drugs safety issue and dissemination to health care professionals and the public | √ | | x | |

| **Core outcome indicators** | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| A percentage of the drug and therapeutics committees that have processed pharmacovigilance activities in the previous year | √ | | x | |
| A percentage of medicinal products passing product quality tests in the previous year | √ | | x | |
| **Complementary outcome indicators** | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
| The existence of risk management plans that are aimed at high-risk medicinal product | √ | √ | x | |
| Pharmaceutical inspection | √ | x | x | |
| Number of data safety requests in the previous year | √ | | x | |
| Percentage of medicinal products safety bulletin published in the previous year | √ | √ | x | |
| Number of drug safety issues identified from international sources | √ | √ | x | |
| Number of “Dear healthcare professional” letters or additional safety alerts and disseminated in the previous year | √ | √ | x | |
| Number of community or public education sessions associated with medicinal products safety processed in the previous year | √ | | x | |
| Percentage of protectable ADRs reported out of the total number of ADRs reported in the last year | x | | √ | |
| Number of medicinal products associated with congenital malformations per 100,000 births | x | | √ | |
| Number of medicinal products identified to be probably related to congenital malformations in the previous 5 years | x | | √ | |

| Complementary outcome indicators | IPAT indicators | Thailand PV new drugs (IPAT) | WHO indicators | Thailand PV new drugs (WHO indicators) |
|---|---|---|---|---|
| Percentage of medicinal products that are counterfeit or substandard in the pharmaceutical market | x | | √ | |
| Number of patients who have the medication errors in the hospital per 1000 admissions in the last year | x | | √ | |
| Average schooldays or work lost because of drug related problems | x | | √ | |
| Cost saving of pharmacovigilance activities | x | | √ | |
| Health financial impact of pharmacovigilance activities | x | | √ | |
| Average number of medicinal products per prescription | x | | √ | |
| The percentage of prescriptions with medicines overdose | x | | √ | |
| The percentage of prescription with the potential drug interaction | x | | √ | |
| The percentage of patients provided information on potential ADRs and how to use the medicines | x | | √ | |

√ (Yes), x (No), Blank (No information)

**Appendix Q-The example of summary report of PV inspection**

**The United Kingdom's experience**

**April 2019 – March 2020**

MHRA conducted 22 inspections during 1 April 2019 to 31 March 2020. Of these 22 inspections, 16 routine inspections were determined with schedule, 5 triggered inspections were assessed the resolution of the critical findings from previous inspections and 1 triggered inspection because of intelligence received. A total of 127 findings, 5 critical findings, 76 major findings and 46 minor findings were detected.

Of 5 critical findings, 3 critical findings were related to the maintenance of the reference safety information, 1 critical finding was associated with additional risk minimization measures and 1 critical finding was related to additional pharmacovigilance activities. For the 3 critical findings, there was the delay in updating the patient information leaflet (PIL), not within the pre-defined timeframe (3- 6 months). One drug company did not implement the educational materials as additional risk minimization measures. Another case was that there was no confirmation of data collected for additional pharmacovigilance activities.



Of those 76 major findings, risk management was the highest proportion with 23 major findings (30%) followed by 20 major findings (26%) of quality management, 14 major findings (18%) of ongoing safety evaluation and 13 major findings (17%) of management of adverse drug reactions.

Of these 46 minor findings, non-compliance was related to 26% of quality management system, 26% of risk management and 15% of ongoing evaluation.

Overall, risk management topics were identified with the highest number of entire findings. Sub-topics included the maintenance of the reference safety information with outdated PIL and SmPC, the management of additional pharmacovigilance activities with the non-compliance of the management of serious adverse events and the non-compliance of QPPV in reviewing and sign-off of the PASS protocol. The non-compliance of additional risk minimization activities include deficiency in implementation of educational materials, non-submission of educational materials for approval and absence of the tracking receipt of the educational materials by the targeted healthcare professionals. The main topics and sub-topics were presented in table1.

**Table 1 The main topics and sub-topics**



| The main topics | Sub-topics |
|---|---|
| **The collection and the collation of adverse drug reactions** | : Spontaneous data sources of safety from medical information and complaints of product quality.<br>: Literature review<br>: Solicited data sources of safety from research.<br>: Safety data exchange agreements |
| **Management of adverse drug reactions** | : Case processing included the data entry, coding, evaluation, the follow-up and reporting ADRs.<br>: Data management included the migration of safety data. |
| **Ongoing safety evaluation** | : Signal management<br>: Periodic safety update reports |

| | |
|---|---|
| **Risk management** | : Maintenance of the reference safety information<br>: Management of the additional pharmacovigilance activities in RMP<br>: Implementation of additional risk minimization measures in RMP<br>: Safety communication<br>: The maintenance of RMP |
| **Quality management system** | : The procedures, the record management, the training, and the pharmacovigilance contracts<br>: The audit and deviation management of the corrective and prevention action (CAPA)<br>: Pharmacovigilance system oversight and governance of the performance monitoring and the role of the qualified person for pharmacovigilance (QPPV)<br>: Applications and information technology systems |
| **Provision of information for supervision by national competent authorities** | : Inspection readiness<br>: Pharmacovigilance system master file (PSMF) management<br>: Submission of information to national competent authorities<br>: Maintenance of information in Extended Eudravigilance Medicinal Product Dictionary (XEVMPD) |
| **Clinical trials pharmacovigilance** | : Clinical trials pharmacovigilance included the maintenance of reference safety information (RSI) for clinical trials and suspected unknown serious adverse reaction (SUSAR) reporting |

## Appendix R-The example of new drugs with RMP and protocols

### Comparison of EU-RMP and US-REMS

The core components of EU-RMP and US-REMS are risk concerned, risk minimization measures and timetable for RMP assessment (post-approval) are presented in table1 and the example of new drugs with RMP are shown in table2. The differences are that EU addresses PASS in RMP whereas US does not include PASS in REMS. US-PASS is mentioned in the review of initial application. The comparison of details of EU-RMP and US-REMS are described as followings:

Risk concerned

All four EU-RMP of new drugs address important identified risks, important potential risks and important missing information as well as US-REMS of Imlygic® while other three US-REMS state only one important identified risk.

Risk minimization measures

Materials including guidance for prescribing, dispensing and patients' brochures are required in both EU-RMP and US-REMS. Particularly, US-REMS provided information regarding the distribution of REMS directly to healthcare professionals. US pharmaceutical companies must send REMS letters via e-mail within 30 days or 60 days of the date a new drug is launched, again 12 months later and report number of healthcare professionals targeted by REMS. Conversely, EU does not mention timing of informing RMP to healthcare professionals. US-REMS requires certified physicians

who pass the prescriber knowledge assessment by answering the questions about new drugs while only Caprelsa® EU-RMP mention that there is the requirement to annually survey to assess physicians' knowledge about educational materials.

Post-authorization safety study

EU requires to submit PASS protocol to European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP). For US, post-marketing requirement and post-marketing commitment are the terms referring to clinical trials and studies that US pharmaceutical companies conduct after authorization. The example of PASS protocol of Imlygic® is displayed in table 3

Timetable for RMP or REMS assessment (post-approval)

The updated EU-RMP could be submitted anytime when new risk occurred or along with PSUR while US-REMS is required at 6 months, 12 months, and annually thereafter from the date of the initially approved REMS.



**Table1 Comparison EU-RMP and US-REMS**

| **Components** | **EU-RMP** | **US-REMS** |
|---|---|---|
| Risk concerned | Important identified risk<br>Important potential risk<br>Important missing information | Important identified risk<br>Important potential risk<br>Important missing information |
| Risk minimization measures | Material<br>: Guidance for prescribing and dispensing<br>Physician<br>: Physician experience in treatment | Material<br>: Medication guide<br>Physician<br>: Certified prescriber |

| Components | EU-RMP | US-REMS |
|---|---|---|
| Risk minimization measures | | Drug company<br>: Send REMS letters via e-mail within 30 days or 60 days of the date new drug launched and again 12 months later and report number of healthcare professionals targeted by REMS |
| Post-authorization safety study | Observational studies and post-marketing clinical trials | US mentioned the requirement of PASS including observational studies and post-marketing clinical trials in the review of initial application |
| Timetable for RMP assessment (post-approval) | Any time when new safety concerned occurred or along with PSUR | 6 months, 12 months, and annually thereafter from the date of the initially approved REMS |

**Table 2 Comparison of EU-RMP and US-REMS of new biologic products: Imlygic®, Blenrep® and new chemical entities: Lojuxta® (EU)/ Juxtapid® (US), Caprelsa®**

| New biologic products | | |
|---|---|---|
| **Imlygic®**<br>**: Talimogene laherparepvec**<br>**: Melanoma** | **EU-RMP** | **US-REMS** |
| Date of approval | 16-12-2015 | 27-10-2015 |
| Risk concerned | Important identified risk<br>: Disseminated herpetic infection in severely immunocompromised individuals<br>Important potential risk<br>: Transmission of Talimogene laherparepvec from patient to close contacts or healthcare providers<br>Important missing information<br>: Pregnancy and lactating women<br>: Pediatric patients | Important identified risk<br>: Disseminated herpetic infection in severely immunocompromised individuals<br>Important potential risk<br>: Transmission of Talimogene laherparepvec from patient to close contacts or healthcare providers<br>Important missing information<br>: Pregnancy and lactating women<br>: Pediatric patients |

| | EU-RMP | US-REMS |
|---|---|---|
| Risk minimization measures | Material<br>: Physician education booklet<br>: Patient safety brochure<br>: Patient alert card<br>Physician<br>: Physician experience in treatment | Material<br>: Medication guide<br>Physician: Certified prescriber<br>Drug company: Provides DHPC and patient brochure to HCP via e-mail within 60 days of approval and annually thereafter 3 years |
| Post-authorization safety study | Observational studies | Post-marketing clinical trials |
| Timetable for RMP assessment (post-approval) | Any time when new safety concerned occurred or along with PSUR | 6 months, 12 months, and annually thereafter from the date of the initially approved REMS |
| **New biologic product** | | |
| **Blenrep®**<br>**: Belantamab mafodotin**<br>**: Multiple myeloma** | **EU-RMP** | **US-REMS** |
| Date of approval | 25-08-2020 | 05-08-2020 |
| Risk concerned | Important identified risk<br>: Ocular toxicity<br>Important potential risk<br>: Nephrotoxicity<br>: Increase risk of infection due to immunosuppression<br>Important missing information<br>: Safety in patients with severe renal impairment<br>: Safety in patients with hepatic impairment | Important identified risk<br>: Ocular toxicity |

| | EU-RMP | US-REMS |
|---|---|---|
| Risk minimization measures | Material<br>: Educational materials for prescribing hematologists, oncologists, eye care professionals and patients<br>Physician<br>: Physician experience in hematology, oncology | Material<br>: Medication guide<br>Physician<br>: Certified prescriber<br>: Go to www.BLENREPREMS.COM to register and complete REMS-Prescriber Knowledge Assessment<br>: The prescribers review prescribing information and answer 9 questions correctly<br>: The prescriber will receive correspondence from the REMS program within 2 business days via e-mail or fax confirming the certification<br>: Conduct ophthalmic examination at baseline prior to taking drugs<br>Drug company:<br>: Send REMS letters via e-mail within 30 days of the date new drug launched and again 12 months later and report number of healthcare professionals targeted by REMS |
| Post-authorization safety study | Post-marketing clinical trials | Post-marketing clinical trials |
| Timetable for RMP assessment (post-approval) | Any time when new safety concerned occurred or along with PSUR | 6 months, 12 months, and annually thereafter from the date of the initially approved REMS |
| **New chemical entities** | | |
| **Lojuxta® /Juxtapid®**<br>**:** Lomitapide<br>: Hypercholesterolemia | **EU-RMP** | **US-REMS** |
| Date of approval | 31-07-2013 | 21-12-2012 |
| Risk concerned | Important identified risk<br>: Hepatotoxicity | Important identified risk<br>: Hepatotoxicity |

| | EU-RMP | US-REMS |
|---|---|---|
| Risk concerned | Important potential risk<br>: Hepatic fibrosis<br>: Primary hepatic tumor<br>: Small intestinal tumor<br>: Pancreatic tumor<br>Important missing information<br>: Pregnancy<br>: Pediatric | |
| Risk minimization measures | Material: Guidance for prescribing and dispensing<br>Physician: Physician experience in treatment | Material: Medication guide<br>Physician<br>: Certified prescriber<br>: Physician reviews Juxtapid® REMS<br>: Physician completes the Juxtapid® REMS Prescriber Knowledge Assessment by answering 8 questions and submit the responses to these questions online to REMS program.<br>Drug company<br>: Send REMS letters via e-mail within 30 days of the date new drug launched and again 12 months later and report number of healthcare professionals targeted by REMS |
| Post-authorization safety study | Lomitapide Observational Worldwide Evaluation Registry (LOWER) | A long-term prospective observational study (product exposure registry) of patients with homozygous familial hypercholesterolemia treated with Juxtapid® (lomitapide) |
| Timetable for RMP assessment (post-approval) | Any time when new safety concerned occurred or along with PSUR | 6 months, 12 months, and annually thereafter from the date of the initially approved REMS |

| **New chemical entities** | | |
|---|---|---|
| **Caprelsa®**<br>**: Vandetanib**<br>**: Thyriod cancer** | **EU-RMP** | **US-REMS** |
| Date of approval | 16-02-2012 | 06-04-2011 |
| Risk concerned | Important identified risk<br>: QTc prolongation and Torsades de pointes<br>Important potential risk<br>: Teeth and bone abnormalities in the pediatric population<br>Important potential risk<br>: - | Important identified risk<br>: QTc prolongation and Torsades de pointes |
| Risk minimization measures | Material<br>: Educational materials for HCP and Patient alert_card<br>Drug company<br>: Annual survey to Caprelsa® prescribers to assess effectiveness of educational materials | Material<br>: Medication guide<br>Physician<br>: Certified prescriber<br>: Physician reviews Caprelsa® REMS<br>: Physician completes the Caprelsa® REMS Prescriber Training Questions and submit the responses to these questions online to REMS program |
| Post-authorization safety study | Multinational, multicenter observational study | - |
| Timetable for RMP assessment (post-approval) | Any time when new safety concerned occurred or along with PSUR | Annually on the date of the initial approval of the Caprelsa® REMS |

**Table 3 PASS protocol of Imlygic®**

| | **EU-Protocol** | **US-Protocol** |
|---|---|---|
| Study design | Multi-national, multi-center observational retrospective chart review study with one-time physician survey | Multi-national, multicenter observational prospective study |
| Study duration | 2017-2019 | 2017-2026<br>(5 years monitoring for each participant) |
| Study setting | Austria, Germany, the Netherlands, the United Kingdom | Austria, Israel, Switzerland, the United Kingdom, and the United States |
| Study population | 66 unresectable Stage IIIB-IVM1a melanoma patients | Estimated enrollment: 920 participants |
| Database | Medical chart review | Electronic health records |

# Appendix S-Abbreviations

| | |
|---|---|
| ACSoMP | Advisory committee on safety of medicinal products |
| ADR | Adverse drug reaction |
| ADRMC | Adverse drug reaction monitoring center |
| APEC | Asia-Pacific economic cooperation |
| AsPEN | Asian pharmacoepidemiology network |
| CNODES | Canadian network for observational drug effect studies |
| CTD | Common technical document |
| EPPV | Early post-marketing phase vigilance |
| EU-ADR | European exploring and understanding adverse drug reactions |
| FDA | Food and drug administration |
| HPVC | Health product vigilance center |
| ICH | International conference on harmonization |
| ICSR | International individual case safety report |
| IPAT | Indicators-based pharmacovigilance assessment tool |
| MedDRA | Medical dictionary for regulatory activities |
| MSH/SPS | Management sciences for health's strengthening pharmaceutical systems |
| NC | New drug with condition |
| OMOP | Observational medical outcome partnership |
| PASS | Post-authorization safety study |
| PEM | Prescription event monitoring |
| PREMA | Pharmaceutical research and manufacturers association |
| PRISMA | Preferred reporting items for systematic reviews and meta-analyses |
| PROTECT | Pharmacoepidemiologic research on the outcomes of therapeutics by the European consortium |
| PSUR | Periodic safety update report |
| RMP | Risk management plan |
| SDMES | Shanghai drug monitoring and evaluation system |
| SMP | Safety monitoring program |
| USAID | The United States agency for international development |
| US FDA | The United States Food and Drug Administration |
| VAESCO | Vaccine adverse event surveillance and communication |
| VISION | Vaccine and immunization surveillance in Ontario |
| VSD | Vaccine safety datalink |
| WHO | World Health Organization |
| WHO-ART | World Health Organization Adverse Reaction Terminology |

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