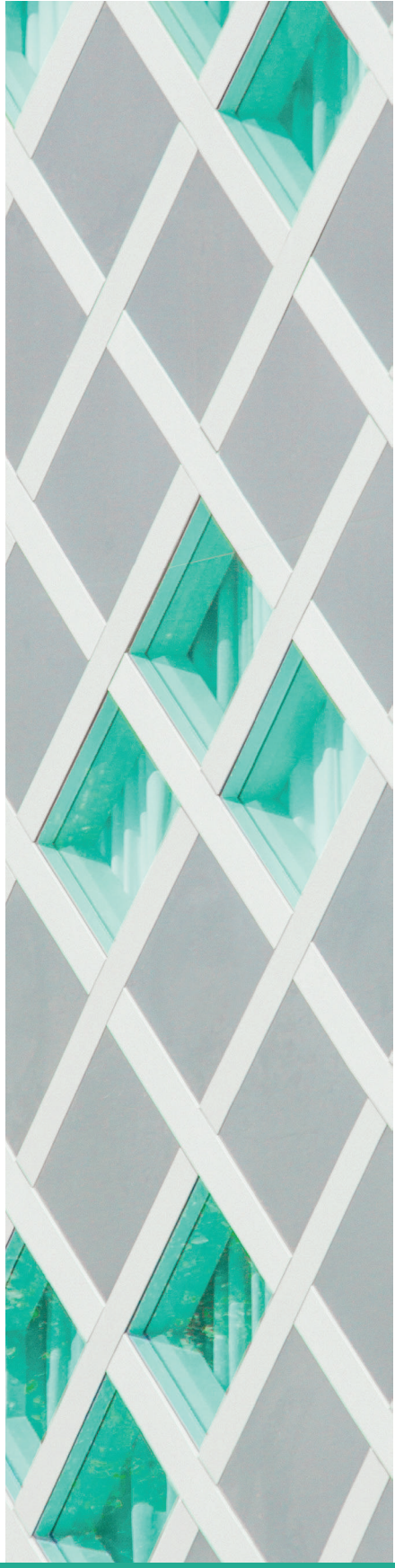
National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

2018
ANNUAL REPORT
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING



Ministry of Health, Malaysia

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING: ANNUAL REPORT 2018

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Our Purpose

Keeping medicines safe for the nation

This is what inspires and drives us as individuals and as a regulatory agency. This is how we contribute to the society by ensuring the safety of the products registered in Malaysia.

Inside this report

The National Centre for Adverse Drug Reactions Monitoring

The National Centre for Adverse Drug Reactions Monitoring serves as a database for all adverse drug reaction (ADR) reports and adverse events following immunisation (AEFI) reports that are submitted to NPRA.

The national centre plays an important role in managing and analysing information on suspected adverse reactions to medicines or vaccines. Based on the evaluation of a safety concern, NPRA may take regulatory action(s) to improve product safety and protect public health, such as updating product packaging information, restricting the use of the product, communicating new safety information to the public, or even removing a product from the market.

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC)

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) was established in 1987 under the Drug Control Authority (DCA) to perform the function of monitoring safety profiles of drugs registered for use in Malaysia.

During MADRAC meetings held once in two months, causality verification is done for all local reports of adverse drug reactions (ADR) as well as adverse events following immunisation (AEFI), and all pertinent drug safety issues are discussed to provide DCA with information and recommendations if required.

A total of **six (6) MADRAC meetings** were held in 2018, with **17,512 ADR reports** presented for verification of causality.

Ex-officio	Chairman **Dr. Ramli Zainal** Director of NPRA
	Secretary **Wan Mohaina Wan Mohamad** Deputy Director, Centre for Post-Registration of Products and Cosmetic Control, NPRA
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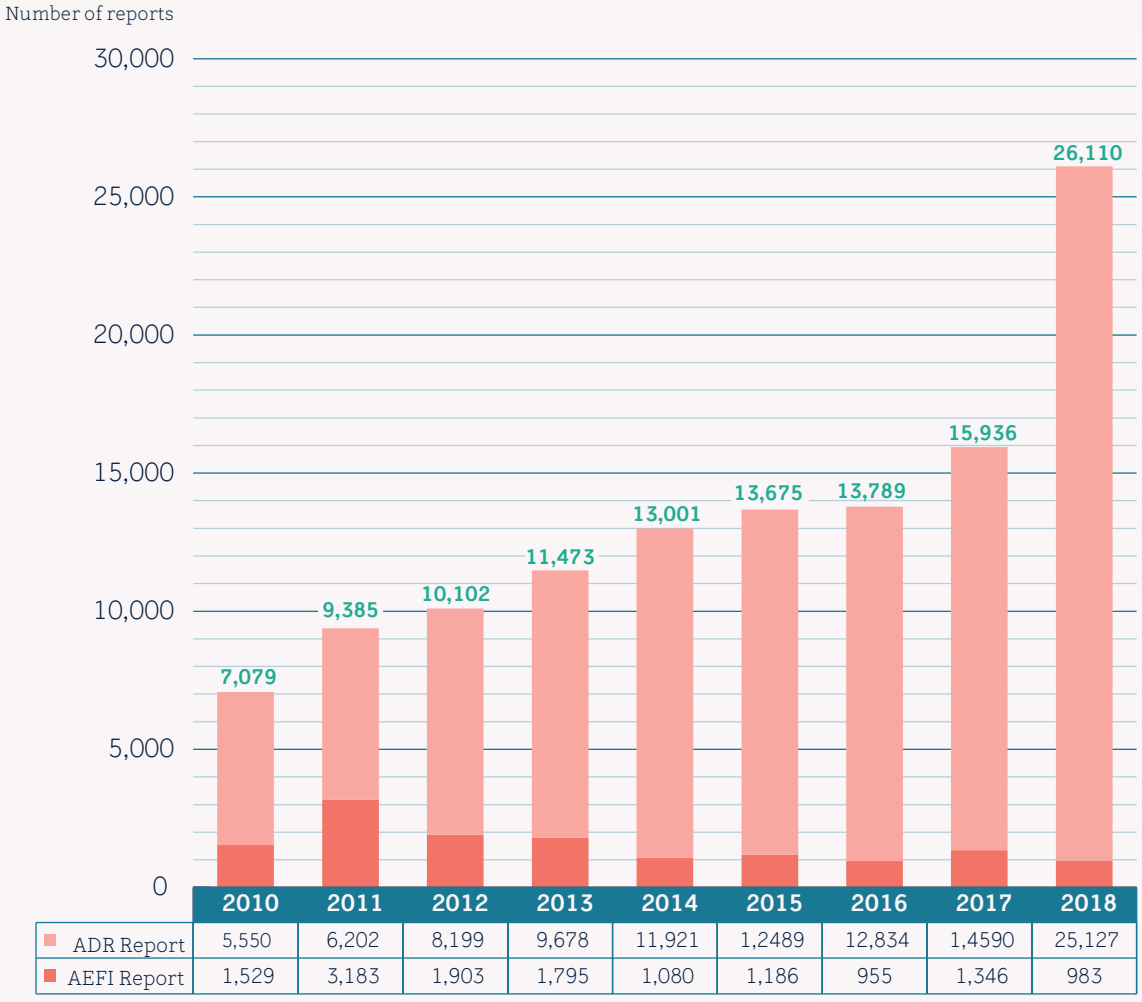
(Lee Seng Dee)

Wan Mohd. Hamidi Wan Sulaiman
Malaysian Pharmaceutical Society (MPS)
(Lee Min Shen)

Analysis of ADR/ AEFI Reports

The National Centre received **26,110 adverse event reports** in 2018, showing a **38.9%** increase from the previous year. Once these reports were processed to exclude any duplicates, follow-up reports to cases sent in earlier, and rejected reports, a total of **23,558 viable new reports** were entered into the Malaysian adverse drug reactions database and sent to the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring in Uppsala, for inclusion into the WHO database.

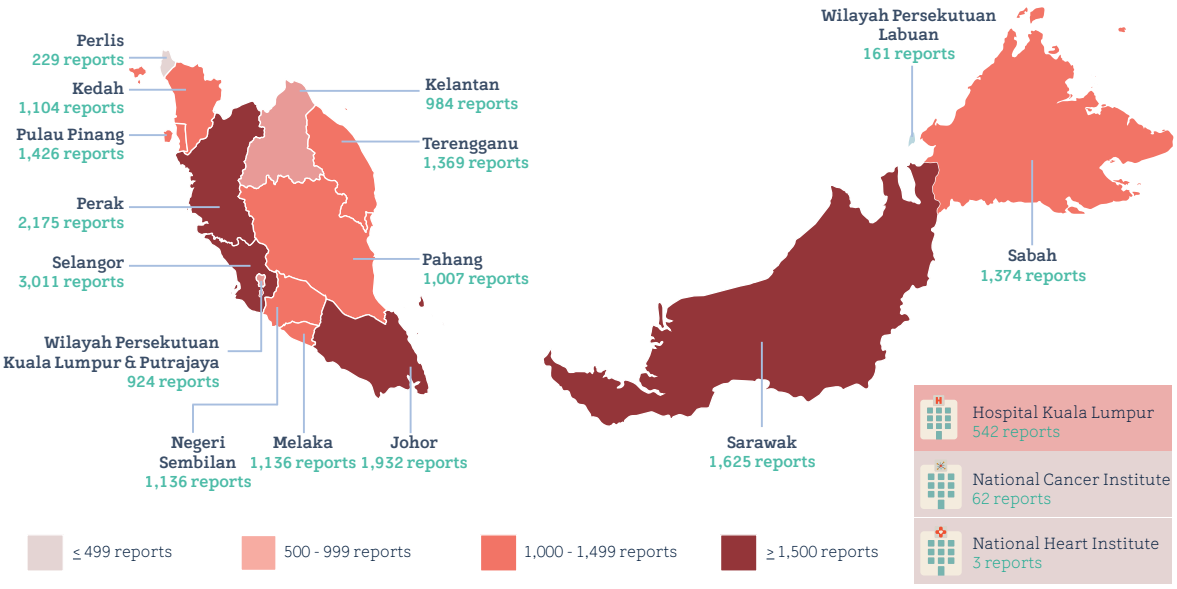
Total Number of ADR and AEFI Reports Received in Malaysia 2010-2018

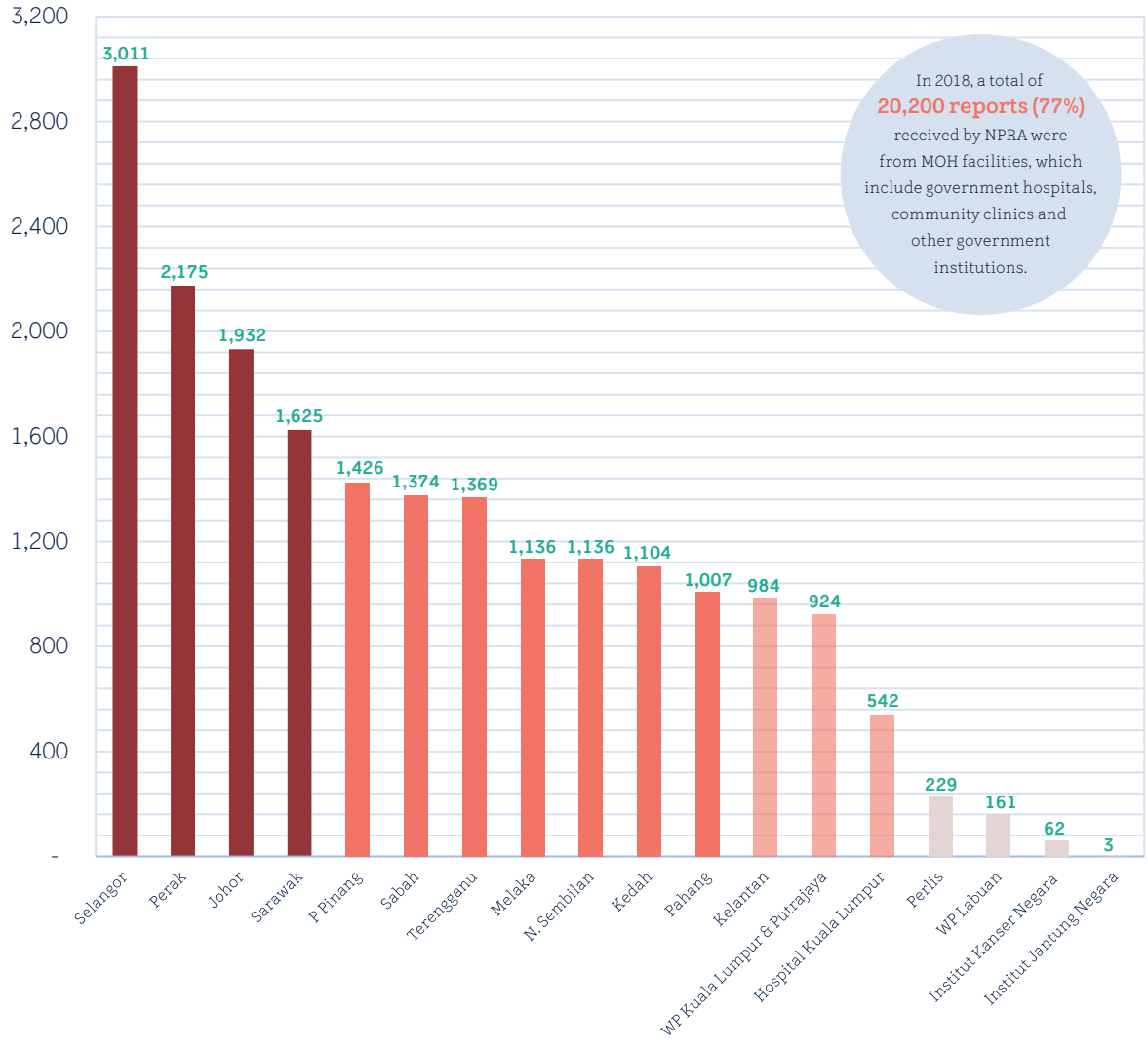


	2010	2011	2012	2013	2014	2015	2016	2017	2018
ADR Report	5,550	6,202	8,199	9,678	11,921	1,2489	12,834	1,4590	25,127
AEFI Report	1,529	3,183	1,903	1,795	1,080	1,186	955	1,346	983

Disclaimer: The figure above shows the number of reports received by NPRA before the full evaluation is carried out. These adverse events are not necessarily causally related to the product.

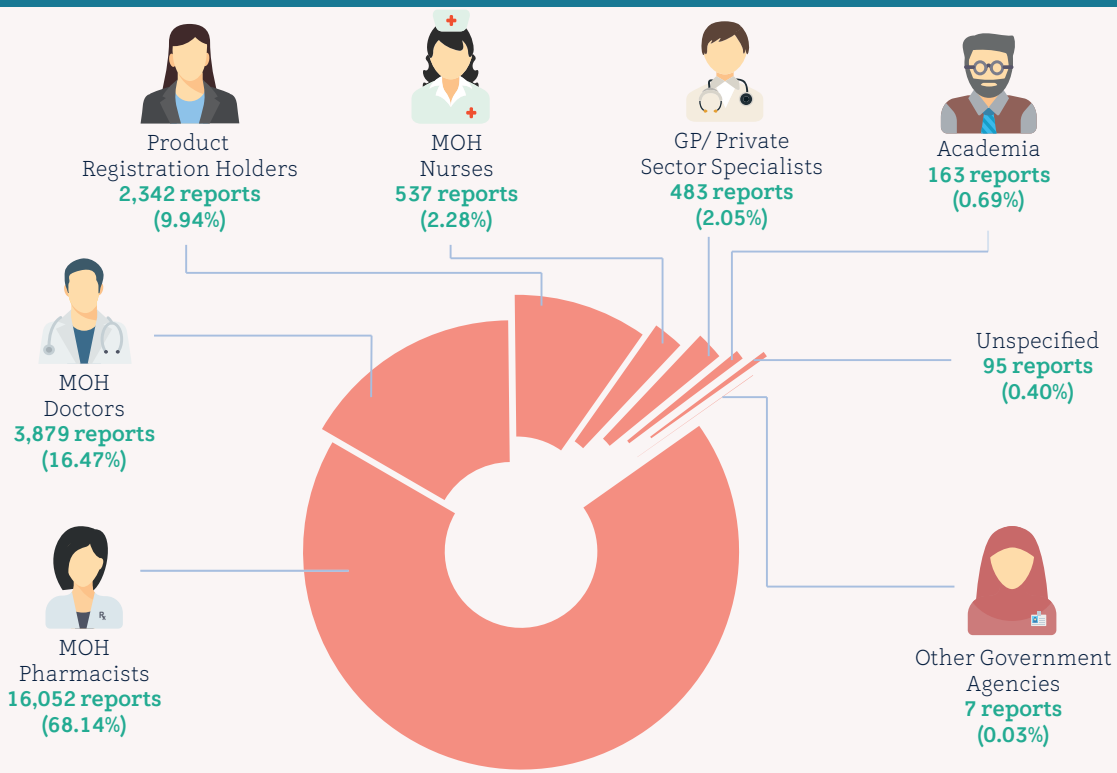
Distribution of ADR / AEFI Reports Received from Ministry of Health (MOH) Facilities, 2018



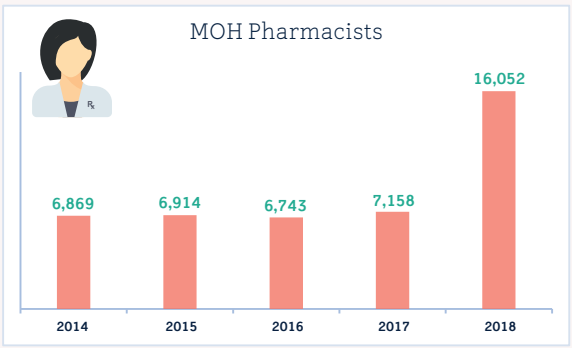


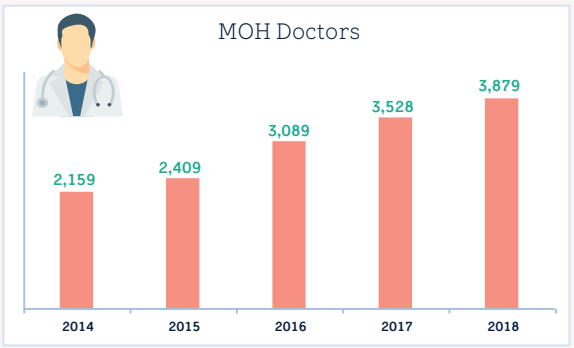
In 2018, a total of **20,200 reports (77%)** received by NPRA were from MOH facilities, which include government hospitals, community clinics and other government institutions.

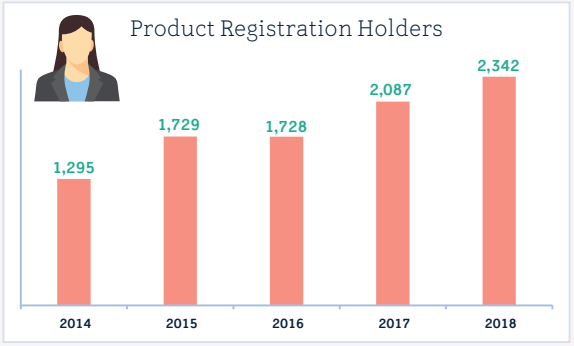
ADR/ AEFI Reports Received by Reporter Category, 2018

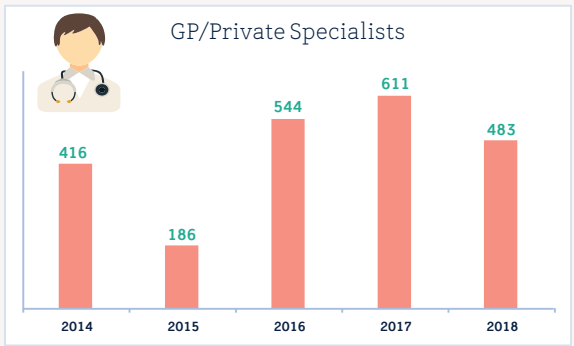


ADR/ AEFI Reports Received by 4 Main Reporter Category 2014-2018









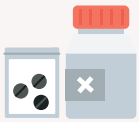
Number of Products Involved in ADR/ AEFI Reports, 2018

23,924
Poisons & prescription items

1,003
Non-poisons

248
Traditional products

59
Food products



209
Unregistered products

ADR/ AEFI Reports Received by Patient's Age Group Category, 2018

16 reports
Neonates less than
1 month old

548 reports
Infants
1 month - 1 year old

2,123 reports
Children
1 - 12 years old

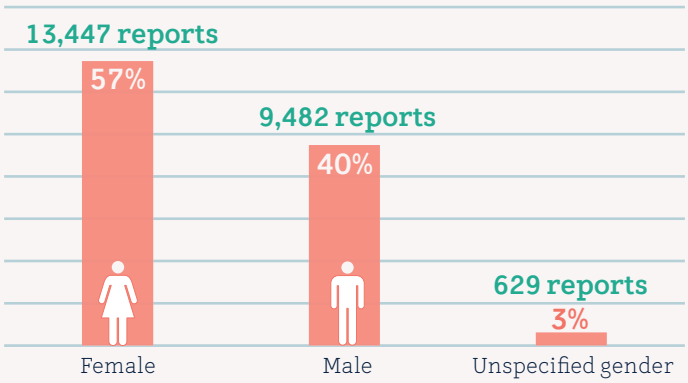
1,054 reports
Adolescents
13 - 18 years old

1,131 reports
Unspecified age

12,977 reports
Adults
18 - 60 years old

5,709 reports
Elderly more than
60 years old

ADR/ AEFI Reports Received by Patient's Gender, 2018



Number of Adverse Drug Reactions Categorised by System Organ Class, 2018

System Organ Class	No. of ADRs
Skin and subcutaneous tissue disorders	15,990
General disorders and administration site conditions	6,997
Nervous system disorders	4,900
Gastrointestinal disorders	4,155
Eye disorders	3,500
Respiratory, thoracic and mediastinal disorders	3,345
Investigations (e.g. platelet count decreased, blood glucose increased)	1,316
Musculoskeletal and connective tissue disorders	843
Cardiac disorders	630
Vascular disorders	449
Infections and infestations	374
Metabolism and nutrition disorders	371
Psychiatric disorders	356
Blood and lymphatic system disorders	265
Injury, poisoning and procedural complications	263
Renal and urinary disorders	257
Immune system disorders	232
Hepatobiliary disorders	230
Ear and labyrinth disorders	131
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	128
Reproductive system and breast disorders	84
Endocrine disorders	63
Pregnancy, puerperium and perinatal conditions	21
Congenital, familial and genetic disorders	16
Surgical and medical procedures	15

2018 Top 10 Most Reported MedDRA System Organ Class

1

Skin and subcutaneous tissue disorders
15,990 ADRs

2

General disorders and administration site conditions
6,997 ADRs

3

Nervous system disorders
4,900 ADRs

4

Gastrointestinal disorders
4,155 ADRs

5

Eye disorders
3,500 ADRs

6

Respiratory, thoracic and mediastinal disorders
3,345 ADRs

7

Investigations
1,316 ADRs

8

Musculoskeletal and connective tissue disorders
843 ADRs

9

Cardiac disorders
630 ADRs

10

Vascular disorders
449 ADRs

Number of Adverse Drug Reactions Categorised by Pharmacological Group, 2018

Pharmacological Group	No. of ADRs
Cardiovascular agents	6,164
Antiinfectives	6,156
Analgesics	3,504
Others	1,232
Antineoplastics	1,173
Vaccines	954
Antidiabetics	830
Traditional medicines	547
Antituberculosis	546
Antiepileptics	525
Antihyperlipidaemics	521
Antipsychotics	341
Antiulcers	328
Antiasthmatics	306
Antiemetics	276
Antigouts	269
Antivirals	243
Anticoagulants	240
Vitamins	215
Antihistamines	184
Hormones	148
Corticosteroids	141
Eye preparations	130
Antidepressants	122
Immunosuppressive agents	111
Health supplements and minerals	96
Contrast media	65
Anaesthetics	42
Dermatologicals	34

2018 Top 10 Most Reported Pharmacological Group

1

Cardiovascular agents

6,164 ADRs

2

Anti infectives

6,156 ADRs

3

Analgesics

3,504 ADRs

4

Others

1,232 ADRs

5

Anti neoplastics

1,173 ADRs

6

Vaccines

954 ADRs

7

Anti diabetics

830 ADRs

8

Traditional medicines

547 ADRs

9

Anti tuberculosis

546 ADRs

10

Anti epileptics

525 ADRs

Monitoring Drug Safety Issues

In 2018, a total of **141 drug safety issues** were identified through environmental screening. Following review, **20 issues were presented at MADRAC meetings** to determine the appropriate risk minimisation measures (refer to page 15-18). The majority of these issues resulted in updates to the package insert safety information, such as tightening of indications or additional contraindications. **Regulatory actions for 20 of these issues** were proposed to the DCA, resulting in DCA directives issued to ensure package inserts of all generic products containing the affected active ingredients are updated with the required safety information.

Besides that, review and approval of safety-related updates to product package inserts were carried out for **367 products (94.3%)** out of 389 applications received.

MADRAC 161 15 March 2018	DCA Directive	DHPC Letter	Product Information Update	Safety Alerts	Further Review
Modified-release paracetamol: Overdose complex and difficulty to manage with modified-release products					●
Ulipristal acetate: Liver injury					●
Pemetrexed: Risk of nephrogenic diabetes insipidus and renal tubular necrosis					●
Methotrexate: Pulmonary alveolar haemorrhage					●
Ofev® (nintedanib): Information on severe liver injury and the need for regular monitoring of liver function in patients with idiopathic pulmonary fibrosis		●	●	●	
Prednisone and prednisolone (excluding topical products): Scleroderma renal crisis	●		●	●	
Mesalazine: Photosensitivity	●		●	●	
Ethinylestradiol: Risk of increased levels of alanine transaminase (ALT) due to intreaction with (i) ombitasvir/paritaprevir/ritonavir combination products; (ii) dasabuvir products	●		●	●	
Carbocysteine and acetylcysteine: Anaphylactic/anaphylactoid reaction and severe cutaneous adverse reactions (SCARs)	●		●	●	
MADRAC 162 26 April 2018					
Hydroxyethyl starch: Suspension due to serious risks of kidney injury and death in certain patient populations				●	●
Iodinated media contrast: Acute generalised exanthematous pustulosis (AGEP)					●
Epilim® (sodium valproate): Annual communication on risk of abnormal pregnancy and serious developmental disorders		●			

	DCA Directive	DHPC Letter	Product Information Update	Safety Alerts	Further Review
Esmya® (ulipristal acetate): Serious liver injury in women using Esmya® for uterine fibroids		●			
Acetazolamide: Severe cutaneous adverse reactions (SCAR)	●		●	●	
Efavirenz: QTc prolongation	●		●	●	
Doxycycline: Jarisch-Herxheimer reaction	●		●	●	
MADRAC 163 7 June 2018					
Noradrenaline: Stress cardiomyopathy					●
Domperidone and clarithromycin: Drug interaction leading to increased risk of QT interval prolongation					●
Stilnox® (zolpidem): Restriction of indication		●		●	
Azithromycin, clarithromycin, erythromycin and roxithromycin: Severe Cutaneous Adverse Reactions (SCARs)	●		●	●	
***Saccharomyces boulardii* products:** Risk of fungaemia	●		●	●	
Iodinated Contrast Media: Severe Cutaneous Adverse Reactions (SCARs)	●		●	●	
MADRAC 164 16 August 2018					
Montelukast sodium: Update on neuropsychiatric adverse reactions - obsessive-compulsive symptoms					●
Apixaban: Drug interaction between apixaban and selective serotonin reuptake inhibitors (SNRI) and/or serotonin and noradrenaline reuptake inhibitors (SNRI) leading to increased risk of bleeding					●

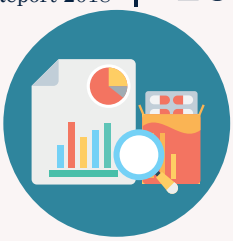
	DCA Directive	DHPC Letter	Product Information Update	Safety Alerts	Further Review
Varenicline tartrate: Loss of consciousness					●
Tivicay® (dolutegravir): Neural tube defects reported in Tsepamo Study, Botswana		●		●	
Xgeva® (denosumab): Risk of new primary malignancy		●		●	
Succinylated gelatin (modified fluid gelatin): Risk of cross-reaction involving allergen galactose-alpha-1, 3-galactose (ALPHA-GAL)	●		●	●	
Isoniazid: Risk of pancreatitis	●		●	●	
Atypical antipsychotic agents: Risk of: (i) Restless leg syndrome (ii) Sleep apnoea (iii) Urinary retention (iv) Hyperglycaemia and diabetes mellitus	●		●	●	

MADRAC 165
18 October 2018

Eltrombopag: Reports of interference with bilirubin and creatinine test results					●
Sodium-glucose cotransporter-2 (SGLT2) inhibitors Fournier's gangrene					●
Tecentriq® (atezolizumab): A new important identified risk - nephritis		●		●	
Esmya® (ulipristal acetate) New contraindication, restricted indication and liver function monitoring requirement		●		●	
Sodium valproate: Risk of congenital malformation and developmental problem in utero-exposed children					●
Pemetrexed: Nephrogenic diabetes insipidus and renal tubular necrosis	●		●	●	

	DCA Directive	DHPC Letter	Product Information Update	Safety Alerts	Further Review
Filgrastim, pegfilgrastim, lenograstim: Aortitis	●		●	●	
Clarithromycin and domperidone: Increased risk of QT interval prolongation	●		●	●	
MADRAC 166 6 December 2018					
Ceftriaxone: Stress cardiomyopathy					●
Acetazolamide: A new contraindication during pregnancy					●
Fluoroquinolones (systemic & inhalation products): Risk of aortic aneurysm and dissection					●
Hydrochlorothiazide: Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma)					●
Epilim® (sodium valproate): Important new contraindications, strengthened warnings and measures to prevent valproate exposure during pregnancy		●		●	
Beta-lactam antibiotics including combination products: Severe cutaneous adverse reactions (SCAR)	●		●	●	
Lamotrigine: Risk of hemophagocytic lymphohistiocytosis (HLH)	●		●	●	

Safety Monitoring of New Products



Periodic Benefit-Risk Evaluation Reports (PBRER)/ Periodic Safety Update Reports (PSUR)

For the first five years of post-registration, product registration holders are required to submit Periodic Benefit-Risk Evaluation Reports/ Periodic Safety Update Reports (PBRERs/ PSURs) on newly registered products, namely New Chemical Entities (NCEs) and biologic products. PBRERs/ PSURs contain information on the product safety profile in countries where it is registered, and any changes or new findings related to product safety.

In 2018, a total of **159 PBRERs** involving **123 products** were assessed, resulting in implementation of package insert changes for **10 products (6.3%)** to ensure that they contain the latest safety information.

Risk Management Plan (RMP)

Product registration holders are required to submit post-registration Risk Management Plans (RMPs) when there is any concern about a risk affecting the benefit-risk balance of a product.

In 2018, post-registration RMPs for **38 registered products** were received, of which **14** were reviewed. In addition, **four (4) educational materials** which consisted of information for healthcare professionals and patients were reviewed and approved. These involved **one (1) biologic product** and **three (3) NCE products**.

Drug Safety Communication

Publications

MADRAC Bulletin

Beginning 2018, MADRAC Bulletin features articles based on local adverse drug reactions / adverse events following immunisation data of a particular drug, followed by a discussion and advice to healthcare professionals. These articles are aimed to capture the interest of healthcare professionals in the clinical setting to help identify adverse drug events, practise caution when prescribing, dispensing or counselling of medicines to patients as well as to encourage ADR/ AEFI reporting. MADRAC Bulletin also keeps its readers up to date with new directives issued to communicate recent drug safety issue, changes in drug prescribing information as well as new warnings and precautions.

NPRA has published and distributed **three (3) MADRAC Buletin issues** in 2018, as follows:

MADRAC Bulletin, Issue 1-2018, Vol. 25
MADRAC Bulletin, Issue 2-2018, Vol. 26
MADRAC Bulletin, Issue 3-2018, Vol. 27

Safety Alerts

Safety Alerts are concise drug-related articles published in the NPRA website which are intended to alert healthcare professionals on new drug safety issues that arise as a result from drug safety reviews by NPRA and other international regulatory agencies. This communication is a form of risk minimisation measure taken to reduce the risk of adverse events of new and existing registered products in Malaysia.

In 2018, NPRA has published **31 safety alerts** to highlight drug safety issues. Click here to see the full list of safety alerts in 2018, which is available on www.npra.gov.my.

Direct Healthcare Professional Communication (DHPC) Letter

Besides the publications above, Direct Health Professional Communication (DHPC) letters, or previously known as "Dear Doctor" letters, are used to communicate recent safety information to healthcare professionals, including important changes in prescribing information, new contraindications, newfound risks and safety issues. Submitted by the product registration holders, DHPC letters are reviewed and approved by NPRA before being distributed.

In 2018, a total of **15 DHPC letters** were approved by NPRA.

ASEAN Post-Marketing Alert System

Developed by the Association of Southeast Asian Nations (ASEAN), the Post-Marketing Alert System (PMAS) functions as a product safety communication sharing system among ASEAN countries for medicinal products, traditional health products and other products. When a safety concern arises, a safety alert will be communicated by the PMAS coordinator of the respective country to ensure the information is distributed to all other ASEAN countries.

The PMAS exchanges information on:

- Products for which registration has been terminated, suspended, or withdrawn due to safety aspects;
- Products recalled from the market due to quality defects with serious public health implications;
- Products found to be adulterated and associated with serious public health implications;
- Significant label changes involving safety;
- New restrictions, on usage, contraindication or prescribing information;
- Exchange of Direct Healthcare Professional Communication (DHPC) letters, media releases related to drug safety, and adverse drug reactions.

In 2018, the Pharmacovigilance Section of NPRA has communicated **36 alerts** via ASEAN PMAS, involving **58 active ingredients** for a total of **713 products**.

Electronic Mailing List

The **NPRA Safety Information Mailing List**, an electronic mailing list, was established in 2014 for healthcare professionals in an effort to ensure wider and faster spread of information. This mailing list is managed by the Pharmacovigilance Section and currently consists of more than 2,000 individuals, including doctors, dentists, pharmacists, nurse, assistant medical officers and assistant pharmacists.

Consumer Medication Information Leaflets

Consumer Medication Information Leaflets, otherwise known as ***Risalah Maklumat Ubat untuk Pengguna (RiMUP)*** are a source of information for consumers, containing advice on how to use the medicines as well as important warnings. RiMUPs are prepared in Bahasa Malaysia and English by product registration holders, and they are reviewed and approved by the Pharmacovigilance Section in NPRA. Approved RiMUPs are uploaded on the NPRA website, and are free for both consumers and healthcare professionals to download.

As of the end of 2018, there were RiMUPs for **1,912 products** available on the NPRA website.

Training and Other Pharmacovigilance Activities

The PMDA-ATC Pharmacovigilance Workshop 2018

The Asia Training Centre for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) had organised a pharmacovigilance workshop at PMDA Office in Tokyo from 5- 8 February 2018. The participants included representatives from pharmaceutical industries as well as regulatory authorities from Azerbajian, Bangladesh, China, Ethiopia, Hong Kong, India, Indonesia, Korea, Myanmar, Nigeria, Papua New Guinea, Philippines, Sri Lanka, Taiwan and Thailand. Two (2) NPRA officers attended this seminar.

The objectives of the seminar were:

- To describe regulatory changes to ensure compliance with new pharmacovigilance, risk management and adverse event reporting initiatives from organisations such as European Medicines Agency (EMA), United States Food and Drug Administration (USFDA), PMDA, and WHO.
- To review risk management plan and risk minimisation activities for important safety specifications.
- To review the method of risk communication for the risk minismisation activities.
- To review the pharmacovigilance plan based on the methods to conduct studies and surveillances.

Vaccine Pharmacovigilance Workshop

On 17- 19 July 2018, in collaboration with the World Health Organisation (WHO), NPRA hosted Vaccine Pharmacovigilance Workshop here at NPRA premises in Petaling Jaya, Selangor. A total of 30 participants have attended this workshop and are from various backgrounds, including the Family Health Division, Disease Control Division and Public Health Division from the Health Ministry, healthcare professionals from hospitals and community clinics, an academician from university as well as several NPRA officers.

Three WHO facilitators, Dr. Shin Jinho, Dr. Syed Fazal Shah and Dr. Ananda Amarasinghe made several presentations covering various topics. Dr. Min-Kyung Kim from Korea Centers of Disease Control and Prevention (KCDC), Republic of Korea also shared her country's experience in vaccine safety and AEFI management system.

The workshop was also followed by a field visit to Putrajaya Precinct 18 Health Clinic to view the vaccine and AEFI management system.

Training Sessions on ADR Report Analysis and Causality Assessment

Further measures are being taken to increase the quality of ADR reports in Malaysia.

With the new pharmacovigilance system and database, as well as continuous training for reporters, it is hoped that more quality and complete reports will be received.

Over the past few years, NPRA has conducted training sessions all across Malaysia on ADR report analysis and causality assessment. In 2018, training was held in Putrajaya, involving 60 participants who were medical officers, consultants and pharmacists. This session was aimed to increase awareness on the importance of reporting, improve the quality of ADR/AEFI reporting, and training reporters to assess causality.

Besides causality assessment training, there were five (5) other training programmes conducted or presentations delivered, which comprised of topics such as pharmacovigilance, adverse events following immunisation (AEFI), and risk evaluation and mitigation strategies.

CPD Points for ADR Reporting by pharmacists

As part of efforts to increase the quantity and quality of ADR reports, in particular from private sector healthcare professionals, beginning January 2016, pharmacists are eligible to claim Continuing Professional Development (CPD) points for the submission of quality ADR reports.

The Pharmacy Board Malaysia has agreed to award one (1) CPD point (maximum of 10 points per year) under category A4 for every ADR report submitted to the NPRA which fulfills certain mandatory criteria [Ref: KKM-55/BPF/101/001/01 JLD 29 (20) and KKM.600-16/1/6(57)].

In 2018, a total of **113 ADR reports** (a 60.9% increment from the previous year) were evaluated and approved for CPD points claim.

***