01.

HEALTH PRODUCTS REGULATION GROUP

We have in place a robust framework for regulating health products, to ensure the highest standards of safety, quality and efficacy.

REGULATORY DEVELOPMENTS AND REVIEWS

We review our regulatory processes regularly to ensure they remain updated and relevant to the latest developments.

OUR WORK DURING THE COVID-19 PANDEMIC

Interim Authorisation via Pandemic Special Access Route (PSAR)

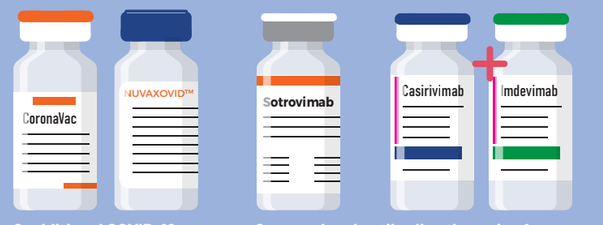
Following the interim authorisation of the first two mRNA COVID-19 vaccines in December 2020 and February 2021, HSA continued to expedite the review of other vaccine types to facilitate diversifying Singapore's vaccine portfolio. This included inactivated and protein subunit COVID-19 vaccines, as well as PAXLOVID™, Singapore's first oral medicine for COVID-19 treatment.

As a condition for interim authorisation under PSAR, companies are required to submit data from ongoing clinical studies for HSA's continual benefit-risk assessment.

In December 2021, HSA also approved the New Drug Application by BioNTech Pharmaceuticals Asia Pacific Pte Ltd for the COVID-19 mRNA vaccine, Comirnaty, to transit from PSAR interim authorisation to full registration.

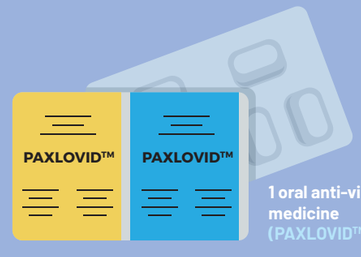
Concurrently, the authorisation of Comirnaty COVID-19 vaccine by Pfizer-BioNTech was extended to children of ages 5 to 11 years.

OVER THE PAST YEAR, HSA GRANTED INTERIM AUTHORISATION FOR:



2 additional COVID-19 vaccines (CoronaVac and Nuvaxovid)

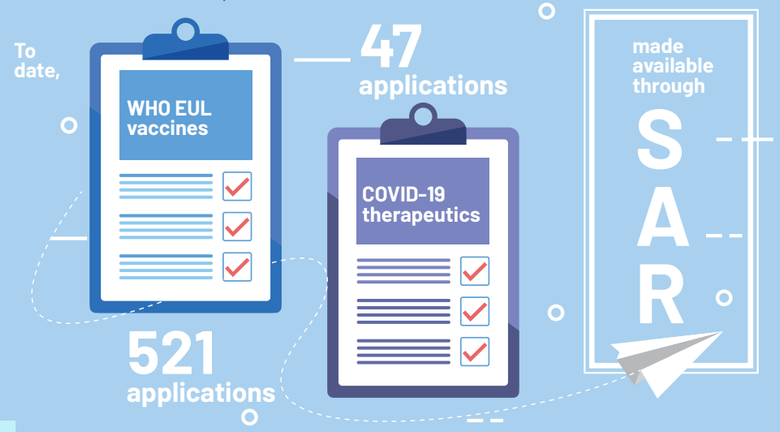
2 monoclonal antibodies therapies for the treatment of COVID-19 (Sotrovimab, combination of Casirivimab and Imdevimab)



1 oral anti-viral medicine (PAXLOVID™)

Facilitating Access to WHO Emergency Use Listing (EUL) Vaccines and Therapeutic Products (TP)

To facilitate access to WHO EUL vaccines which have not been authorised under the PSAR by HSA, the Special Access Route (SAR) was put in place in June 2021. This SAR allows healthcare institutions to bring in unauthorised vaccines as an alternative to PSAR-authorised vaccines to cater to the needs of their patients.



Expediting Clinical Trials

We continued to play a critical role in providing early regulatory guidance and following up closely with companies that are developing COVID-19 vaccines in response to emerging SARS-CoV-2 variants.

Through prioritising and expediting the review of COVID-19 clinical trials, we helped to bolster Singapore's capabilities to develop vaccines and therapeutics quickly and efficiently to manage the global pandemic.

Piloting Remote Good Clinical Practice (GCP) Inspections

As COVID-19 safe management measures meant that physical GCP inspections could not be carried out, we successfully piloted and conducted remote virtual GCP inspections in 2021.

With the virtual inspections, we were able to ensure that the safety and well-being of trial participants were safeguarded, and that the clinical trial data was credible.

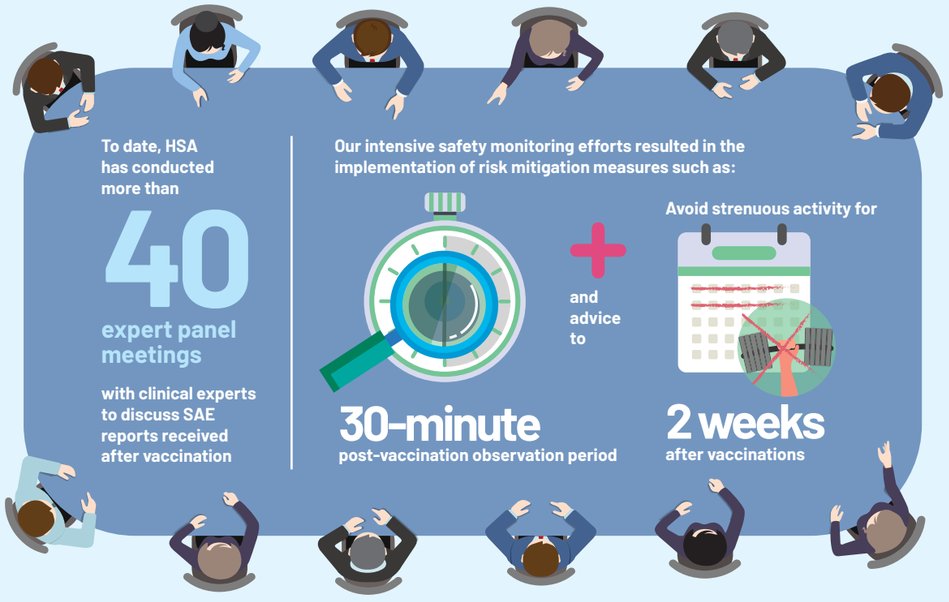
Active Safety Monitoring of Vaccines

HSA initiated its most intensive vaccine safety monitoring effort to date with an enhanced safety monitoring framework for COVID-19 vaccines. The aim of this exercise was to ensure that any emerging safety concerns associated with vaccines could be detected and managed promptly to protect public health. This in turn ensured that the benefits of vaccines continue to outweigh any known risks.

Initiatives that were rolled out under this framework included:

- Expedited reporting of serious adverse events (SAE) by healthcare professionals
- Consumer self-reporting of adverse events (AE)
- Appointment of clinical experts in the different disciplines of neurology, cardiology, rheumatology, haematology and nephrology to adjudicate SAEs of interest received locally

We also worked with key stakeholders including the Ministry of Health and the Health Promotion Board to leverage electronic medical records and the National Immunisation Registry records for the active surveillance of COVID-19 vaccines. With these data points, we were able to enhance our detection of potential safety concerns, using data analytics, as well as epidemiology studies.



Ensuring Regulations Remain Relevant and Responsive

To safeguard the rights, safety and well-being of trial participants, the Health Products (Clinical Trials) Regulations was amended in October 2021. Updates included:

- New requirements to inform trial participants whenever human tissue is collected
- Enabling appropriately qualified and trained pharmacists to be principal investigators of clinical trials that involve locally registered TPs, subject to safeguards and requirements

Facilitating Access to Medical Devices

As of 31 March 2022, we granted marketing authorisation for 273 COVID-19 diagnostic test kits.

Enhancing Consumer Safety Awareness

To enhance consumer safety awareness when purchasing masks, we published a list of locally manufactured medical masks that meet 95% Bacterial Filtration Efficiency on the HSA website for easy reference.

Enhancing Communications to Healthcare Professionals and Public

Given the speed at which COVID-19 vaccines and treatments are being developed and made available to the public, rapid communication of information on newly authorised COVID-19 vaccines and treatments to healthcare professionals is crucial.

Accordingly, HSA has published monthly safety updates on COVID-19 vaccines on our website since April 2021. Rare SAEs identified with the COVID-19 vaccines that have been highlighted in these safety updates include anaphylaxis and myocarditis.

STREAMLINING AND ENHANCING OUR PROCESSES

To ensure regulatory efficiency, we are always looking for new ways to streamline and enhance our work processes.

FINALISED GUIDANCE ON E-LABELLING OF TPs

In April 2021, after consultation with industry and healthcare professionals, HSA finalised and implemented the guidance for the e-labelling of approved package inserts and patient information leaflets for prescription-only TPs.

E-labelling not only allows for efficient and timely dissemination of the latest approved product information, it is also eco-friendly. Our next step would be to review the feasibility of extending e-labelling to non-prescription TPs.

To date, e-labelling has been implemented for over

400

prescription-only TPs

NEW AND UPDATED GUIDELINES

Updating of Guidelines for Traditional Medicines (TM) and Heath Supplements (HS)

In March 2022, the updated safety, quality, labelling and claims guidelines for TM and HS were finalised and published on our website. These guidelines provide good practices for the industry to level up relevant standards and ensure that the products that companies deal with are of good and consistent quality.

The guidelines were published after HSA held discussions with and solicited feedback from industry experts and relevant associations.

New and Refined Guidelines for Medical Devices

a. *3D-Printed Medical Devices (Jul 2021)*

We came up with a guideline and accompanying Frequently Asked Questions on HSA's regulatory perspectives and risk-based approach for the control of medical devices manufactured using 3D-printing technology.

b. *Unique Device Identification (UDI) Framework (Aug 2021)*

To support Singapore's adoption and implementation of UDI used internationally to enhance patient safety and streamline the tracking and identification of medical devices, we:

- Published guidance documents to provide clarity on the regulatory requirements and framework for UDI implementation, and
- Enhanced our systems to cater for UDI and ease of device information record keeping

c. *MD Product Classification Guide (Nov 2021)*

We refined this guide to provide greater clarity on a list of commonly enquired products, and to present their classifications clearly.

d. *Regulatory Reference Agency Approvals (Jan 2022)*

We updated the list of medical device reference regulatory agencies that HSA recognises for abridged, expedited or immediate review. The updated list now includes US FDA's De Novo, the updated EU Medical Device Regulations (MDR) and IVD Regulations (IVDR).

Guidance for Local Manufacturers and Distributors

May 2021

We published a new Guidance Note with a list of Frequently Asked Questions and interpretation of Good Manufacturing Practice (GMP) guidelines to clarify the regulatory requirements for companies performing secondary packaging for therapeutic and medicinal products.

Oct 2021

We delivered two presentations to 15 Chinese Proprietary Medicines manufacturers at the Complementary Health Products Industry Training Workshop 2021. These presentations provided updated guidance and expectations on regulatory requirements.

Dec 2021

We published the results of our monitoring and trend analysis of deficiencies observed during GMP and Good Distribution Practice (GDP) inspections of licensed and certified manufacturers and distributors. Through the sharing of the results, the industry will be better able to focus on key improvement areas.

Jan 2022

Leveraging feedback from the industry, we published a comprehensive Guidance Note on the licensing, GMP certification and inspection of TP manufacturers. This Guidance Note seeks to facilitate the industry's understanding of regulatory processes and requirements.

TAPPING ON TECHNOLOGY

We tapped on technology to better serve our stakeholders and improve our efficiency.

FORMSG FOR SPECIAL CONSIGNMENT

In January 2022, we used FormSG to launch a user-friendly web-based form to simplify the application process for special consignments. The purpose of this process is to allow companies to divert stock from other markets to mitigate potential stock-out situations in Singapore, and to ensure the continued availability of registered TPs.

LAUNCHING OF AUDIT MANAGEMENT SYSTEM (AMS)

We launched the AMS for GDP and retail pharmacy inspections in January 2022. The AMS digitalises GDP and pharmacy audit-related work processes such as arranging for inspections, scheduling and communicating with companies on inspection findings.

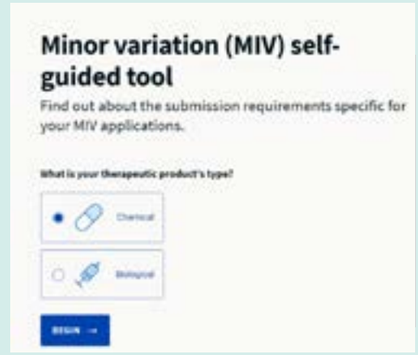
Inspectors can now use handheld devices to review company information and document findings in the AMS, thereby enhancing the inspection processes and improving our connection with stakeholders.

To ensure a smooth transition to the new process, we will continue to monitor the system and engage with stakeholders on a regular basis.

SELF-HELP TOOLS

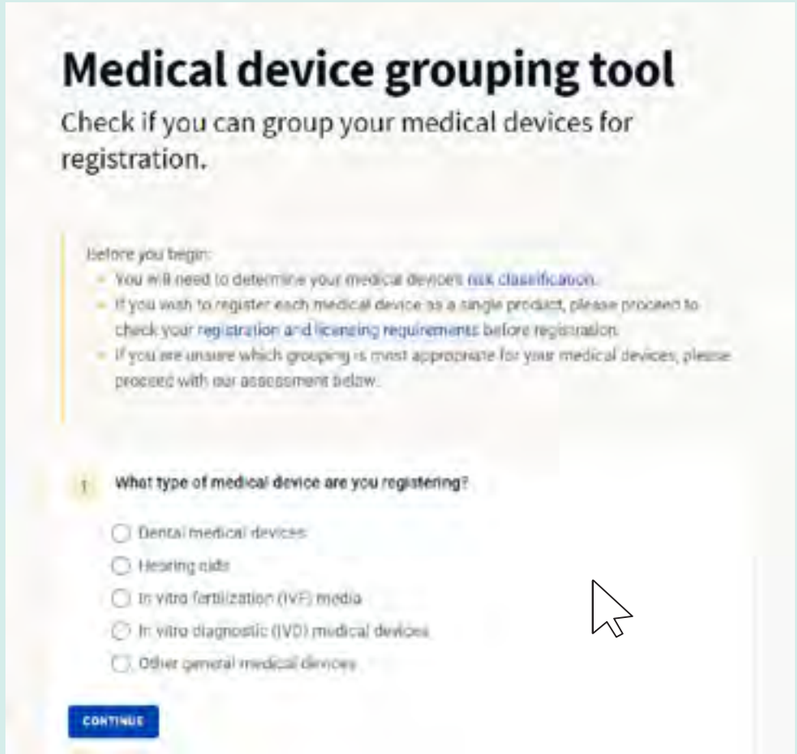
TP Post-approval Minor Variation (MIV) Tool

The MIV tool enables applicants to quickly determine the correct application type, variation category and documentary requirements for their TP MIV applications in just a few clicks. By gaining a better understanding of the regulatory process for good quality submissions, stakeholders can benefit from a more expedient application process.



Medical Device Grouping Tool

We launched a new medical device grouping tool in February 2021 for users to quickly and easily ascertain which medical devices can be grouped together for pre-market registration preparation. Grouping allows certain medical devices to be included in a product registration submission to reduce cost and effort.



STAYING VIGILANT

To ensure public safety, we are committed to staying vigilant at all times.

LOCAL THERAPEUTIC PRODUCT DEFECT CASES

In FY21/22, a total of:

213 local defect cases were received from various sources

Of these, the top 3 issues reported were related to:

- Product packaging **60** cases
- Manufacturing **52** cases
- Product contamination **38** cases

HSA worked with the companies to ensure that appropriate corrective and preventive actions were taken to mitigate the impact on the safety and quality of the defective products as well as their future batches.

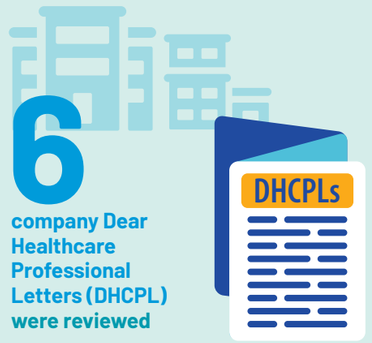
Regulatory actions taken included

- **27** amendments to product registration
- **24** communications issued
- **22** product recalls

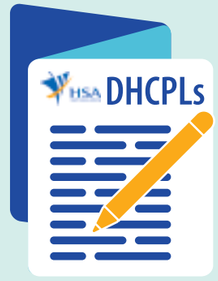
ADVISORIES ISSUED

9 press releases were issued including safety advisories on **18** products

6 company Dear Healthcare Professional Letters (DHCPL) were reviewed



5 DHCPLs were issued by HSA



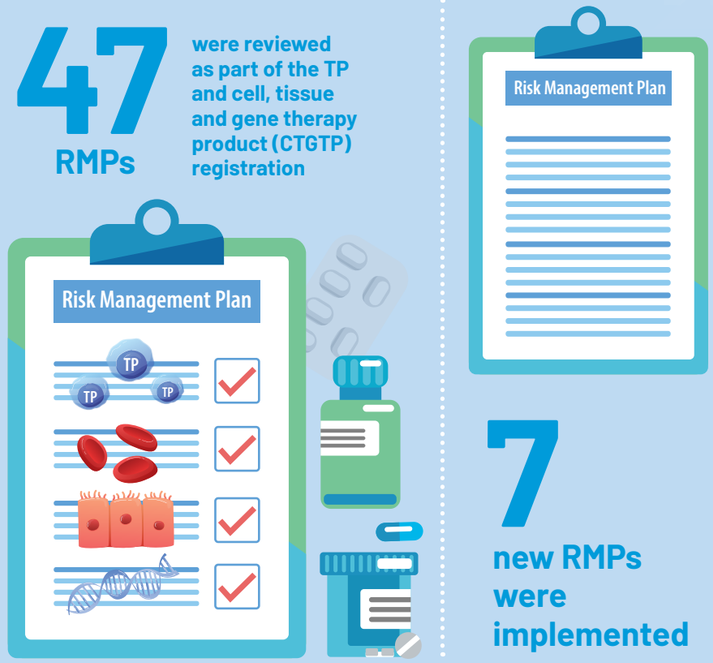
3 HSA ADR News Bulletins were published and disseminated to registered healthcare professionals

12 safety updates were published on the HSA website

UPDATE ON PRODUCT RISK MANAGEMENT

Singapore-Specific Risk Management Plans (RMP)

47 RMPs were reviewed as part of the TP and cell, tissue and gene therapy product (CTGTP) registration



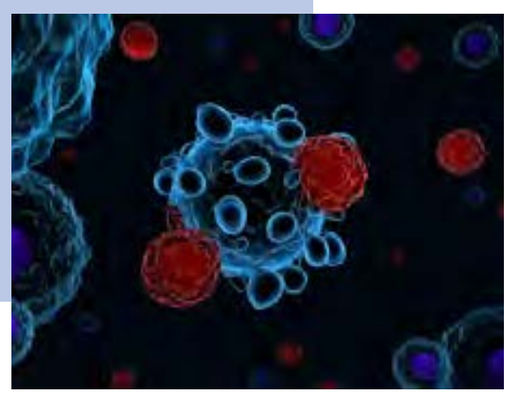
7 new RMPs were implemented

Enhanced RMPs for CTGTPs (Kymriah® and Luxturna®)

Enhanced RMPs were put in place to manage safety concerns, such as cytokine release syndrome, neurotoxicity, and infections associated with the first two CTGTPs approved locally.

This resulted in:

- A controlled distribution programme and site qualification at treatment centres
- Provision of educational materials for healthcare professionals, patients, and product administration personnel
- Close monitoring of the products' safety profile through submission of long-term safety studies and periodic benefit-risk evaluation reports



Safety Signals

TP and CTGTP

157 safety signals were assessed as part of post-market pharmacovigilance activities

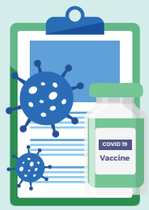
This resulted in:

- Amendment of local package inserts to reflect newly emerging safety concerns
- Communication of product safety information in the form of DHCPLs, HSA's Adverse Drug Reaction (ADR) News Bulletin, and product safety alerts on HSA's website

COVID-19 Vaccines and Therapies

Enhanced safety monitoring of COVID-19 vaccines and therapies, and their evolving safety profiles resulted in:

21 monthly safety summary reports on COVID-19 vaccines reviewed



6 monthly safety summary reports for COVID-19 therapies reviewed

Adulterated Health Products

7 risk assessments were conducted on adulterated products, resulting in the issuance of press releases to warn the public

MEDICAL DEVICE POST-MARKET SURVEILLANCE AND VIGILANCE SYSTEM

Adverse Events

In FY21/22, a total of

778

local reporting of adverse events were received

Top 3 medical speciality areas from which the reports were received

Cardiovascular:

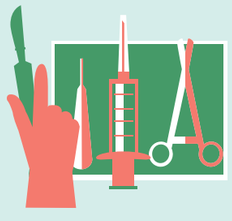
308

Devices under this specialty include implantable cardioverter-defibrillators/ pacemakers, external defibrillators, cardiovascular stents

General Hospital:

134

Devices under this specialty include infusion pumps, patient monitors, ventilators



General & Plastic Surgery:

79

Devices under this specialty include breast implants, dermal fillers, surgical staplers

Field Safety Corrective Action (FSCA)

HSA also worked with the companies to ensure that appropriate corrective and preventive actions were taken to mitigate the impact on the safety and quality of the defective medical devices as well as their future batches.

Total number of FSCAs:

593

Recalls: **66**

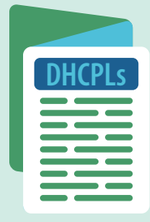
Safety corrective actions: **222**

Dissemination of additional safety information: **305**

Advisories Issued

DHCPL

35



Press release

1

Safety alerts and updates

9

SHARING OUR KNOWLEDGE

To raise the standards of health products regulation in Singapore, we share our knowledge and expertise with our partners and stakeholders.

TALK ON REGULATION OF IVDs AND PRECISION MEDICINE PRODUCTS AT DUKE-NUS CENTRE OF REGULATORY EXCELLENCE (CORE)

We were invited to deliver a talk on the regulatory developments and advancements on In Vitro Diagnostics (IVD) regulations for the DUKE-NUS' CoRE Graduate Certificate in "Health Products Regulation: In Vitro Diagnostics and Precision Medicine" programme. The topics we spoke on included total product lifecycle, international and ASEAN frameworks, as well as post-market and regulatory requirements for next generation sequencing-based IVDs and companion diagnostics.

CONTINUING PHARMACOVIGILANCE EDUCATION INITIATIVES

We collaborated with the following local and international working groups and organisations on various pharmacovigilance education initiatives:

Local

Date	Collaborators / Event	Topic
Jan 2021	Duke-NUS CoRE	Regulation of CTGTPs
Apr 2021	Saw Swee Hock School of Public Health	Risk communications training
Oct 2021	Duke-NUS CoRE	Principles and framework for pharmacovigilance
Nov 2021	Roadshows for Nanyang Technological University graduates in Double Degree in Bachelor of Sciences in Biomedical Sciences and Bachelor of Chinese Medicine	Raise awareness among the Traditional Chinese Medicine community on HSA's adverse event monitoring efforts

International

Date	Collaborators / Event	Topic
Sep 2021	Duke-NUS CoRE: World Health Organization (WHO) Uppsala Monitoring Centre (UMC) -HSA Inter-regional Pharmacovigilance Training Workshop	Enhancing preparedness for pharmacovigilance
Oct 2021	Coalition to Accelerate Patient Engagement in Asia-Pacific (CAPE) Regional Multi-stakeholder Roundtable	Patient engagement
Nov 2021	WHO UMC's Medsafety week	Importance of reporting vaccine adverse effects

NEW LOCAL PARTNERSHIPS

We are committed to building up our partnerships with local agencies and companies.

COLLABORATING WITH HOME TEAM SCIENCE AND TECHNOLOGY AGENCY (HTX) ON CONTRABAND PRODUCT SURVEILLANCE

In a bid to crack down on contraband products sold online in a more accurate and effective way, and to further safeguard public health, HSA began trialling an automated e-commerce surveillance tool developed by HTX.

The use of robotic process automation and artificial intelligence to trawl through listings of illegal drugs, health products and cosmetics, as well as unauthorised COVID-19 test kits and vaccines has shortened the process to a matter of hours, instead of weeks taken previously. The automated process also helped to free up manpower as enforcement officers had to manually sift and analyse one listing at a time prior to this initiative.

ENGAGING HEALTHCARE PROFESSIONALS ON COVID-19 VACCINE SAFETY SURVEILLANCE

In August 2021, we participated in the Pharmaceutical Society of Singapore's Continuous Professional Education Session to share on the topic of "Regulatory Updates on COVID-19 Vaccines in Singapore", which included HSA's Pandemic Special Access Route and the safety surveillance of COVID-19 vaccines. A total of 351 pharmacists attended and we received positive feedback that participants had benefitted from the session.

PUBLISHING OUR ADR NEWS BULLETIN ON AGENCY OF INTEGRATED CARE'S (AIC) WEBSITE

In our efforts to ensure effective communication of health products safety information to healthcare professionals, we collaborated with AIC to publish our ADR News Bulletin and relevant AE Guides on their website regularly. This will enhance our drug safety communications to General Practitioners in over 1,000 CHAS clinics island-wide.

INTERNATIONAL COLLABORATIONS

Beyond our shores, we collaborate with various organisations to strengthen our knowledge base.

COMPLETION OF PILOT PROJECT WITH KOREA MFDS

Building on the Memorandum of Understanding signed with Korea's Ministry of Food and Drug Safety (MFDS) on GMP for Pharmaceutical Products in November 2019, we embarked on a one-year pilot project to establish mutual confidence in each party's GMP inspection regulatory framework.

The pilot project was successfully completed in July 2021, with both parties concluding on the equivalency of the frameworks. This paves the way for MFDS and HSA to rely on the GMP certificates issued by either side without the need for any additional inspections on local manufacturers, and thereby enhance regulatory efficiency.

MFDS and HSA are now working towards formalising the arrangement through a Mutual Recognition Agreement.

SINGAPORE REGISTERED MEDICAL DEVICES ELIGIBLE FOR ABRIDGED REGISTRATION PROCESS IN THE PHILIPPINES

As of November 2021, under the Philippines Food and Drug Administration's (FDA) regulatory reliance programme, medical devices (Class B, C or D) approved by HSA using the Common Submission Dossier Template are now eligible for the abridged registration process. Companies can leverage HSA's medical device approvals for faster entry into the Philippines market.

HSA-NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA) COLLABORATION

In June 2021, we approved the first application under our ongoing collaboration with Malaysia's NPRA on the evaluation of generic medicines.

PROJECT ORBIS

Project Orbis is a collaborative effort that seeks to provide a framework for concurrent submission and review of oncology products among international regulatory health authorities. Collaborators include the Brazilian Health Regulatory Agency, Health Canada, Israel's Ministry of Health, Swissmedic, Australia's Therapeutic Goods Administration, US FDA's Oncology Centre of Excellence, and UK's Medicines and Healthcare Products Regulatory Agency.

Through Project Orbis, HSA has issued regulatory approvals for

7
applications

INTERNATIONAL MEDICAL DEVICE REGULATORS FORUM (IMDRF)

Medical Device Single Audit Programme (MDSAP)

In April 2021, we were recognised as an Affiliate Member of the IMDRF MDSAP, paving the way for future full-fledged membership. This programme recognises the Auditing Organisation's regulatory audit of medical device manufacturers as a single requirement for multiple member jurisdictions.

AE Working Group

In September 2021, we chaired the IMDRF AE Working Group meetings. Our objective was to improve, harmonise and expand the terminology used to code information relating to medical device AEs.

WHO MEMBER STATE MECHANISM RISK COMMUNICATION WORKING GROUP

We continued to work with the WHO to enhance the ability to run effective risk communication campaigns for substandard and falsified medical products in WHO member states.

ACCESS CONSORTIUM

Access is a coalition of like-minded regulatory authorities, whose aim is to provide patients with timely access to high quality, safe and effective TPs in the member countries.

Through Access, we:

Published
4
joint statements

on Access' regulatory position on COVID-19 vaccines and therapeutics

Completed review of
9
TP applications

through work sharing collaborations

CLAMPING DOWN ON ILLEGAL ACTIVITIES

We embarked on various enforcement operations to clamp down on illegal health products and tobacco-related activities.

COMBATTING CYBERCRIME TO SAFEGUARD PUBLIC HEALTH

We collaborated with various stakeholders to detect the illegal sale of health products on local e-commerce platforms.

Through our efforts, a total of:

6,054
illegal health product listings were removed

2,759
advisories were issued

REVOCATION AND SUSPENSION OF TOBACCO RETAIL LICENCES

We took action against stores selling cigarettes to those below the Minimum Legal Age (MLA)

and suspended the licences of

2 offending retail outlets

ILLEGAL HEALTH PRODUCTS

Multi-agency Enforcement Operation

In October 2021, we participated in a multi-agency enforcement operation led by Bedok Police Division and supported by the Criminal Investigation Department, Central Narcotics Bureau (CNB), Immigration & Checkpoints Authority, Singapore Customs and Singapore Food Agency.

Through this operation:

3
men between the ages of 32 and 43

were rounded up for investigation

Cough syrups, assorted brands of sexual enhancement medicines and other illegal medicines worth a street value of about:

$16,000
were seized

OUR OVERALL ENFORCEMENT RESULTS

426
joint operations with Singapore Police Force and CNB

were conducted

An estimated $572,993

worth of health products were seized

33
suspects

were rounded up for investigation

OPERATION PANGEA

In May 2021, we participated in Operation Pangea – an enforcement operation by the International Criminal Police Organisation (INTERPOL) targeting the online sale of illegal pharmaceutical products. In the intensive one-week operation, HSA stepped up its surveillance of local e-commerce platforms.

Over **700** listings of illegal health products (prescription medicines, adulterated weight loss, sexual enhancement and cosmetic products) were removed

14th year that HSA has been involved in Operation Pangea

92 countries took part

SMUGGLING OF ELECTRONIC VAPORISERS (E-VAPORISERS)

May 2021

An illegal seller caught using four different social media platforms to advertise and sell e-vaporisers and related components was sentenced on 31 May 2021 with a fine of $53,500.

OUR OVERALL E-VAPORISER ENFORCEMENT RESULTS

30 e-vaporiser peddlers prosecuted

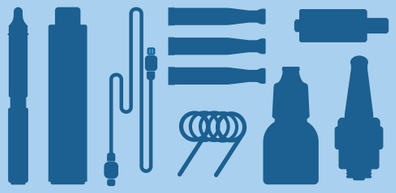
Youngest offender: **18** years old (sentenced to 24-month probation)

Range of fines meted out:
$1,500 – $40,500

Total amount of fines:
$283,100

June 2021

We carried out investigations following the detection of illegal smuggling of e-vaporisers and related components at Tuas Checkpoint by ICA officers. In this case, e-vaporisers and related components were found to be concealed in the seats of lorries used to transport live chickens.



54,392 units of e-vaporisers and related components were seized

Street value

~$700,000

Suspects involved:

14 drivers and attendants

Ages of smugglers:

22 to 54 years

Sentencing terms:

up to 2 months

October 2021

Acting on a tip-off, HSA raided a storage facility in Boon Lay. The successful operation marks the largest-ever seizure of e-vaporisers and related components by HSA, in terms of the volume and street value. It also disrupted the operations of an illegal e-vaporiser supply chain.

Total street value of seized items

Over **$2.2 million**

AWARDS AND ACHIEVEMENTS

Our efforts were validated through the following awards and achievements.

ACHIEVING WHO ML4 STATUS

With effect from 17 January 2022, HSA became the first national regulatory authority to be awarded the highest recognition of Maturity Level 4 for operating an advanced medicines regulatory system. This achievement comes after a rigorous and comprehensive assessment by a team of international assessors using WHO's Global Benchmarking Tool.

This external validation by WHO will enhance the Singapore public's confidence and trust in HSA as an innovative and effective medicines regulator working to protect and advance public health and safety.

PRO-ENTERPRISE INITIATIVE AWARDS 2021

Gold Award

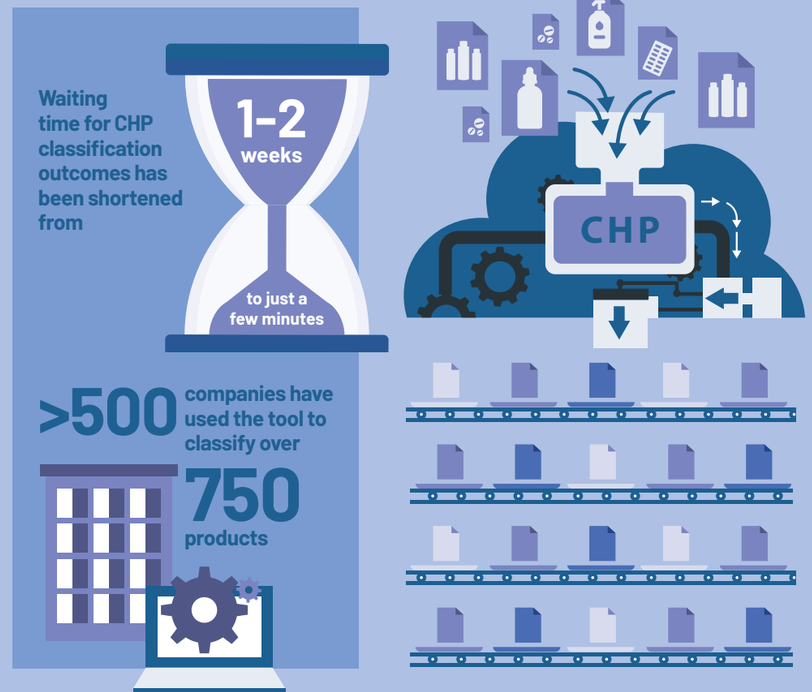
During the pandemic, HSA implemented various initiatives, including regulatory pathways, consultations and virtual audits to support our local businesses, as well as ensure continued and prompt access to critical therapies and medical devices.

For our efforts in ensuring that our population would be one of the earliest in the world to have access to critical COVID-19 vaccines, medicines and medical devices, we received the Gold Award at the Pro-Enterprise Initiative Awards 2021.

Bronze Award

For our efforts in coming up with the digital Complementary Health Products (CHP) Classification Tool to enable the industry to self-determine the classification of their products, we received the Bronze Award at the Pro-Enterprise Initiative Awards 2021.

Through our enhanced CHP Classification Tool:



HSA also won three Public Service Transformation (PST) Awards 2021, including the Agility Award 2021, for our regulatory agility and facilitation in supporting Singapore's fight against COVID-19, and ensuring that Singapore had timely access to diagnostic tests, medicines and vaccines. For more details, please refer to *page 80*.