Australian Government
Department of Health
Therapeutic Goods Administration

Regulation in times of a pandemic

[This is not mainly a presentation on GMP]

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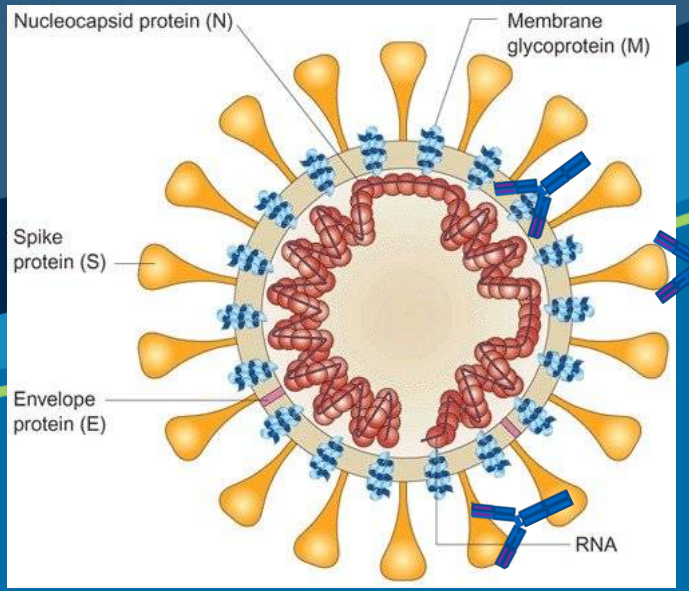
GMP Forum May 2021

12/05/2021



Regulatory flexibilities and performance during the pandemic

The purpose of regulatory flexibilities

- To facilitate development and access to COVID-19 medicines, vaccines, IVD, PPE and devices
- Managing medicine, PPE and device shortages during the COVID-19 pandemic period and related lockdowns
- To facilitate continuity of regulatory services during COVID-19 related restrictions

Redirection of our resources during COVID had limited impact on business as usual

Prescription medicines	July-Dec 2019	July-Dec 2020
NCC/NCE/biosimilar TGA median review time	201 working days	**182 working days**
Category 1 review time	169	**152**
Category 1 approvals	181	**188**
SAS cat B approvals	27714	**45820**
Australian GMP inspections	80	64
Overseas GMP inspections	41	15
GMP clearances approved	2874	**3317**
Medicines recalls managed	32	**47**

Medicine shortages/discontinuations

Unprecedented times

- Stockpiling led to a **sharp increase in demand** for medicines in March 2020
- Most **international and domestic passenger flights cancelled** – these carry the bulk of medicines
- TGA received a **double the usual number** of shortage notifications in April 2020 (282 vs 150) – but returned to normal levels soon after
- Concerns re supplies of medicines for ventilated **intensive care unit patients**

Medicine shortages/discontinuations

Unconventional approaches

- **5 times the usual number of s19A approvals** to supply an overseas-registered product
- **Medicine Shortages Working Party** identified and developed coordinated solutions
- **ACCC exemption** - meetings to explore **coordinated approaches** to managing supply of critical medicines
- Worked with DFAT and Austrade to address **export restrictions and logistics issues**
- Control and **impose limits on purchase of medicines** to avoid out of stock situation
- Implemented **dispensing and prescribing controls**, e.g. of salbutamol, analgesics, hydroxychlorquine
- Receiving **data on supplies of critical medicines** from sponsors and jurisdictions to support monitoring
- **Serious Shortage Substitution Notices** allowed pharmacists to substitute a different strength or dose form for a medicine in shortage without prior approval from the prescriber
- Worked with state and territory health departments to **model demand for ICU medicines**

Medicine and vaccine authorisation and access

Unprecedented times

- Willingness to **try unapproved therapies** in the very ill under hospital ICU supervision
- Importance of patient access to approved medicines and vaccines **as soon as deemed safe and effective**
- Needed to **enable clinical trials to continue** under social distancing and travel constraints

OTC Medicines

Unprecedented times

- Greatly **increased demand for hand sanitisers**
- **Panic buying of OTC analgesics**, stocks stranded overseas

Unconventional approaches

- **Excluded Goods determination** for specified hand sanitisers, which excluded from TGA regulation that contain
  - only certain ingredients in particular quantities
  - comply with certain manufacturing practices
  - with advertising, labelling and presentation requirements
- **Expedited applications** for relevant products

Enquiries and support for new sponsors

Unprecedented times

- **Flood of enquiries** April-June 2020
  - General enquiries to TGA up by 250%
  - Medicines Shortages enquiries up by 300%; OTC medicines by 180 %
  - Medical Devices information line call volumes increased by over 200%
  - Compliance referrals increased by 150 %
- Many enquiries were from **potential new sponsors who had not marketed therapeutic goods before**

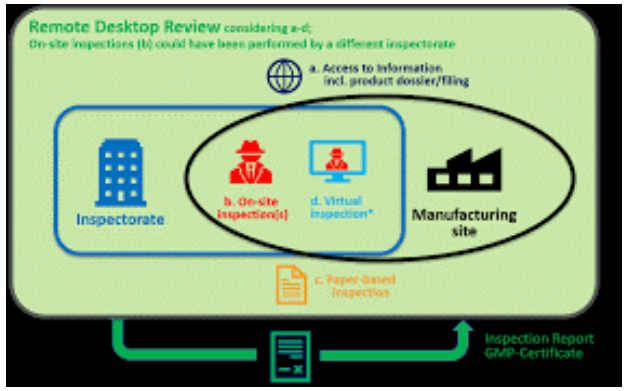
Unconventional approaches

- **Stronger partnerships** with established sponsors enabled rapid patient access to products
- Active involvement in national taskforce for ventilators, test kits and PPE
- **Provision of scientific advice** to new and established sponsors
- **Support provided 7 days a week** during first national COVID wave

Good Manufacturing Practice

Unprecedented times

- All **international GMP inspections** postponed
- **Domestic inspections** highly constrained
- **Domestic shipping** of pharmaceuticals constrained



Unconventional approaches

- **Remote "virtual" and hybrid** inspections
- Increases in the number of **GMP clearance applications**
- **Regulatory amendments** made to enable hospitals to manufacture radiopharmaceuticals for the treatment of a patient in another State or Territory

The importance of vaccine GMP during a pandemic

Need for rapid expansion of global manufacturing capacity presents many challenges:

- **Increased reliance on Contract Manufacturing Organisations** – New relationships and jurisdictions as well as limitations in the number of CMO's available
- **Supply chain constraints** – limitations in suppliers of raw materials
- **Technology transfer** – Several sites around the world are being brought online together
- **Cross contamination** – Multiple products manufactured in the same facilities
- **Public Scrutiny** – increased pressure on manufacturers to deliver

Robust adherence to GMP principles can help mitigate many of these risks

COVID-19 Impact on GMP for regulators

GMP oversight has been significantly impacted

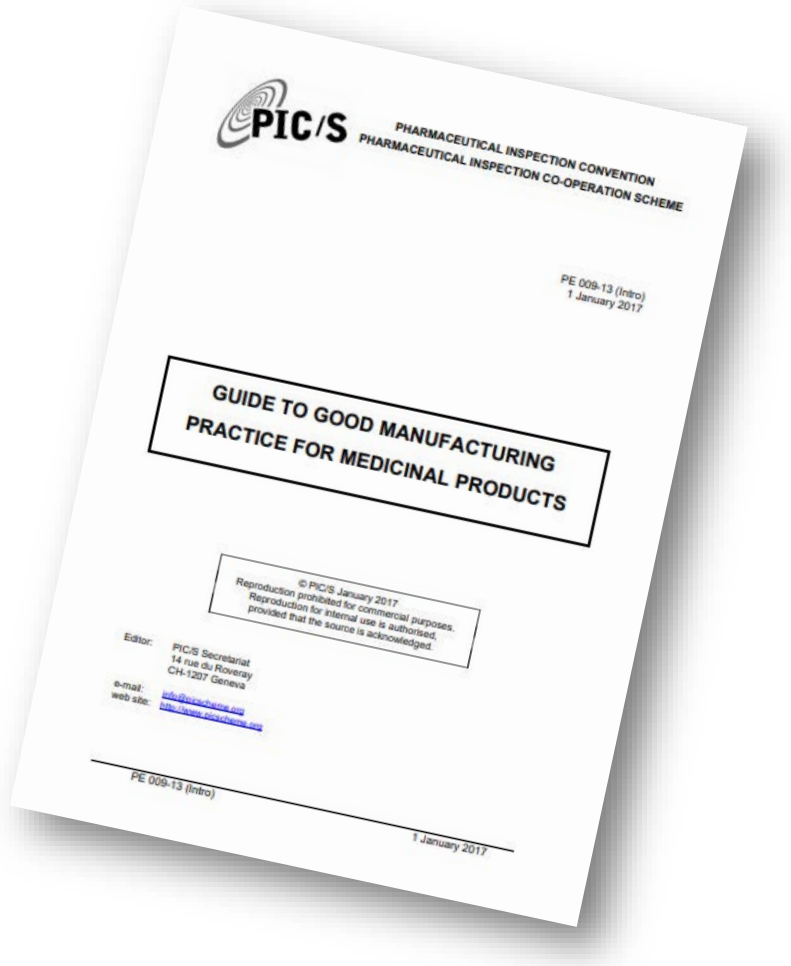
- The ability to perform routine **on-site inspections** of manufacturers affected
- Increased **inspection reliance** adds pressure on existing regulatory frameworks
- **Remote or Virtual GMP inspections** adds complexity for regulators especially for overseas manufacturers
- **Compliance and monitoring** impacted with a reduction in routine GMP signals

For **GMP Clearances** this has meant:

- Increased **collaboration with MRA partners** and acceptance of ‘distant assessment’ certificates
- **Aligning expiry dates** in line with published industry guidance
- New **GMP Clearance questionnaire** to bridge gap since the last on-site inspection
- **Requesting additional documents** as required – a more involved assessment
- Providing additional time for sponsors and manufacturers to address assessment questions

TGA's response to the COVID-19 impact on GMP

- **March 2020** – Suspension of overseas GMP inspections
- **April 2020** – introduction of the domestic remote or hybrid GMP inspection processes
  - ➢ over 130 remote and 148 hybrid inspections performed
- **July 2020** – Introduction of alternative evidence requirements for the GMP Clearance framework
- **July 2020** - announcement of overseas remote inspection process
  - ➢ about 40 performed since August 2020


PIC/S
PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME
PE 009-13 (Intro)
1 January 2017
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Compliance and Enforcement

Unprecedented times

- **Everyone wants to make a quick buck out of COVID-19 !!!**
- **COVID "cures"** promoted by construction businesses, TV celebrities, "churches", clothing companies
- **Inappropriate advertising** of IVD kits, hand sanitisers, disinfectants, masks, other devices and complementary and prescription medicines
- Illegal importation or supply of IVD test kits, PPE and certain medicines

Unconventional approaches – to April 30 2021

- **1,565 COVID-19 advertising cases** for investigation
- **2,052 COVID-19 import and other compliance** cases - 692 warning letters issued in relation to imports
- **370 contacts with advertisers** – warning or cease and desist letters, education letters and direction notices
- **143 infringement notices** issued ($1.51 m) and one matter before the Federal Court (Oxymed Australia PL)

Master Chef host fined $ 25,200 by TGA

“Church” selling miracle cure fined $ 151,200 by TGA

Medicine and vaccine authorisation and access

Unconventional approaches

- **Emergency exemptions** enabled certain unapproved medicines to be procured for National Medical Stockpile
- Much **earlier and ongoing engagement with industry and researchers** on trial design, manufacturing requirements, especially vaccines
- **Commitment by governments** to purchase vaccines before they receive regulatory approval
- Priority processing of **COVID CTNs** by TGA and no need to notify certain trial variations to TGA
- **Rolling submissions, simultaneous reviews** by teams, rapid review (e.g. of remdesivir, vaccines)

Unprecedented international collaborations

- **Weekly dialogue between regulators** on:
  - efficacy and safety data requirements for vaccines
  - information on vaccine safety
  - vaccine confidence and communications
  - how regulators may evaluate vaccines for variants
  - vaccines in pregnancy and in adolescents
  - new and experimental therapies and COVID tests
  - remote inspections of manufacturing facilities
- Joint or **collaborative product evaluations**
- **Mutual Enforcement Operations** (TGA/Border Force /international agencies) targeting imported counterfeit COVID-19 therapeutic goods

The regulatory scheme is also constantly under review

House of Reps Inquiry into the approval processes for new drugs and novel medical technologies in Australia

Pandemic seen as an opportunity to seek longer term system improvements

Inquiry is reviewing:

1. **The range of new drugs and emerging novel medical technologies** including areas where there is an interface between drugs and novel therapies
2. **Incentives to research, develop and commercialise new (or repurposed) drugs and novel medical technologies for conditions where there is an unmet need**
3. **Measures that could make Australia a more attractive location for clinical trials**
4. **Whether the approval process for new drugs and novel medical technologies, could be made more efficient**, including through greater use of international approvals, alignment of registration and reimbursement processes or post market assessment

Main points in submissions relevant to the TGA

(many more submissions were focussed on reimbursement and clinical trials)

- **Lack of knowledge** of TGA's facilitated medicines and device evaluation pathways
  - priority and provisional review
  - use of Comparable Overseas Regulator reports, ACCESS work-sharing and FDA Project Orbis
- Provide **fee waivers and vouchers** for rare or paediatric diseases
- Specific TGA guidance, incentives and a bespoke **pathway for repurposing medicines**
- Use **Patient reported outcomes/ Real world evidence** more widely in medicines evaluations
- Improve **regulatory – reimbursement linkages**
- Clearer guidance on clinical trials/CTX and GMP requirements for **gene and cell therapies**
- Different regulatory category and GMP pathway for **nuclear medicines**

The new normal – lasting impacts on regulation ?

- **Nimbleness** – work sharing, reliance, more facilitated pathways, exemptions, notifications rather than pre-approvals – which should endure ?
- **Strengthened linkages** – with public health and HTA bodies
- **Patient engagement** – greater interest in personal/public health

- **Regulator as facilitator** – increasing trend, accelerated by COVID
  - information on the regulatory scheme – RAS, SME Assist
  - provision of scientific advice
  - rolling data submissions and more pre-submission meetings
  - joint meetings on regulation and funding/procurement
  - GMP support for new facilities

Teachers also coach and encourage students but at the end of the term fail those students if warranted – will require culture change

Coach and mentor

Judge

COVID-19 vaccines

What vaccine data does TGA review ?

Efficacy

- Types and level of immune responses induced by the vaccine
- Clinical trials - must very significantly reduce COVID-19 in large numbers of subjects vs controls

Quality

- Manufacture according to international standards of good manufacturing practices (GMP).
- Manufacturing process at each production site - well controlled and consistent.
- Data on the identity and purity of the vaccine components and its potency, and on vaccine stability
- Batches and documentation undergo evaluation by TGA laboratories before they can be supplied

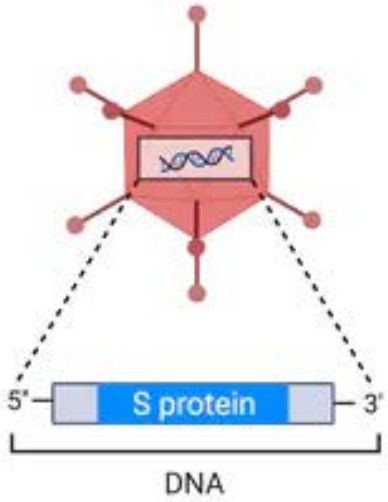
Safety evidence

- Toxicology data from experimental animals
- Both common and infrequent side effects need to be reported in the regulatory submission
- Participants in clinical trials must be followed for at least 2 months after final vaccine dose
- Safety experience of other countries where vaccine may already be in use

Safety and effectiveness is also continuously monitored after vaccine approval

COVID vaccines procured by Australia
(in addition we have access to 25.6 m COVAX doses)

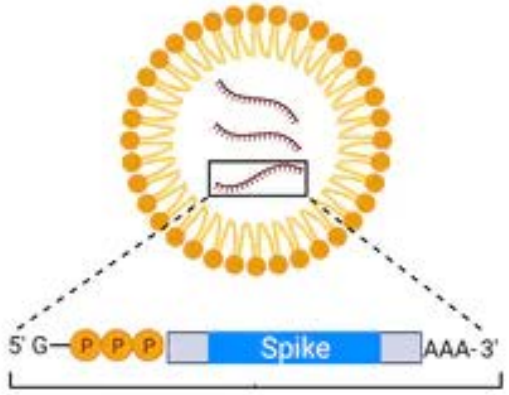
Vaccine: University of Oxford/ AstraZeneca



Platform: Adenovirus with gene for the SARS-CoV-2 spike (S) protein

Approved 15 Feb 2021
53.8m doses purchased

BioNTech/Pfizer



Platform: lipid nanoparticle-encapsulated mRNA vaccines encoding Spike protein

Approved 24 Jan 2021
40 m doses purchased

Novavax

Platform: Synthetic nanoparticle coated with trimer spike protein. Matrix M used an immune-boosting adjuvant

Data still being submitted to TGA
51 m doses purchased (Biocelect)

https://theconversation.com/what-is-novavax-australias-third-covid-vaccine-option-and-when-will-we-get-it-157227

Transparency is critical for public confidence

At the time of approval of each vaccine, TGA publishes extensive information

- Product Information – for hospitals, GPs and pharmacists
- Consumer Medicine Information – for the public
- Decision summary - overview of evaluation process
- Australian Public Assessment Report - considerations that underpinned approval
- Advice from the Advisory Committee on Vaccines

Weekly safety summaries and updates on specific safety issues are also published

Safety signal detection and investigation

Monitor Vaccine Safety

Information comes from

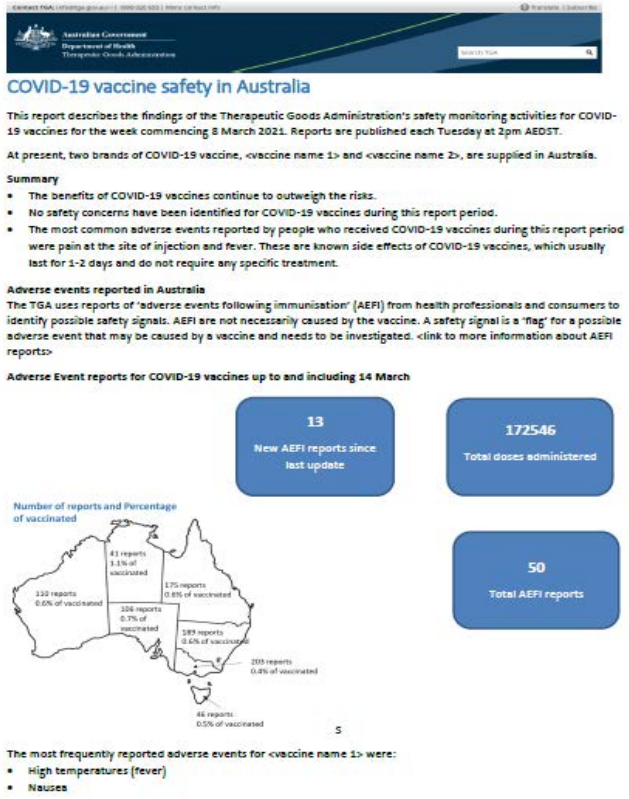
- Adverse event reports from GPs, public, industry
  - GP vaccination agreements - reporting of AEFIs
  - Global industry and international regulators
  - Text message follow up of certain vaccinated people

How are the signals analysed ?

- By event type, patient age, location, batch number
- Comparing observed vs expected “background” rates
- Causality is key vs the same age/ co-morbidity cohort
- Expert panel reviews causality for new serious events

Safety communication is key to vaccine confidence

– weekly dashboards, media statements



COVID-19 vaccine safety in Australia

This report describes the findings of the Therapeutic Goods Administration's safety monitoring activities for COVID-19 vaccines for the week commencing 8 March 2021. Reports are published each Tuesday at 2pm AEDST.

At present, two brands of COVID-19 vaccine, <vaccine name 1> and <vaccine name 2>, are supplied in Australia.

Summary

- The benefits of COVID-19 vaccines continue to outweigh the risks.
- No safety concerns have been identified for COVID-19 vaccines during this report period.
- The most common adverse events reported by people who received COVID-19 vaccines during this report period were pain at the site of injection and fever. These are known side effects of COVID-19 vaccines, which usually last for 1-2 days and do not require any specific treatment.

Adverse events reported in Australia

The TGA uses reports of 'adverse events following immunisation' (AEFI) from health professionals and consumers to identify possible safety signals. AEFI are not necessarily caused by the vaccine. A safety signal is a 'flag' for a possible adverse event that may be caused by a vaccine and needs to be investigated. <link to more information about AEFI reports>

Adverse Event reports for COVID-19 vaccines up to and including 14 March

13
New AEFI reports since last update

172546
Total doses administered

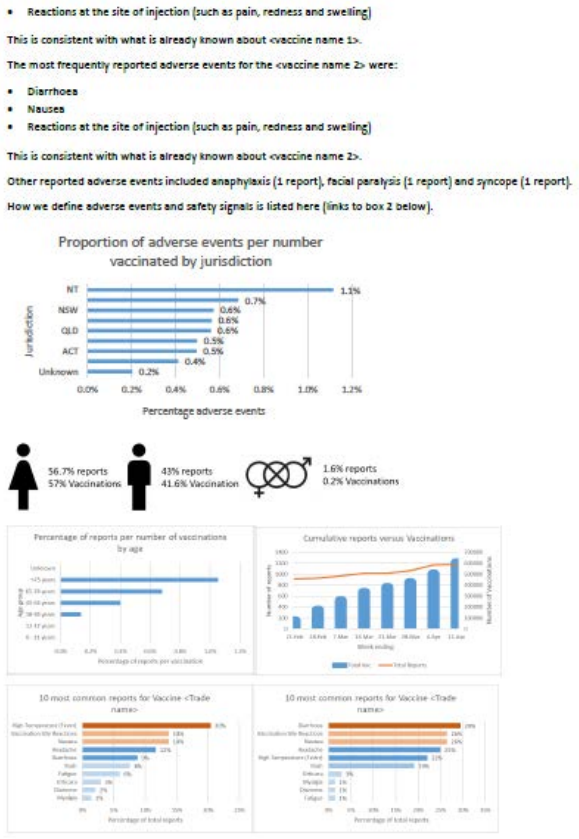
50
Total AEFI reports

Number of reports and Percentage of vaccinated

5

The most frequently reported adverse events for <vaccine name 1> were:

- High temperatures (fever)
- Nausea



- Reactions at the site of injection (such as pain, redness and swelling)

This is consistent with what is already known about <vaccine name 1>.

The most frequently reported adverse events for the <vaccine name 2> were:

- Diarrhoea
- Nausea
- Reactions at the site of injection (such as pain, redness and swelling)

This is consistent with what is already known about <vaccine name 2>.

Other reported adverse events included anaphylaxis (1 report), facial paralysis (1 report) and syncope (1 report).

How we define adverse events and safety signals is listed here (links to box 2 below).

Proportion of adverse events per number vaccinated by jurisdiction

56.7% reports
57% Vaccinations

43% reports
41.6% Vaccination

1.6% reports
0.2% Vaccinations

Percentage of reports per number of vaccinations by age

Cumulative reports versus Vaccinations

10 most common reports for Vaccine <Trade name>

10 most common reports for Vaccine <Trade name>

AstraZeneca ChAdOx1-S COVID-19 vaccine

Updated safety advisory – rare and unusual blood clotting syndrome (thrombosis with thrombocytopaenia)

8 April 2021

The TGA has previously published about the AstraZeneca COVID-19 vaccine and blood clots and included information in this week's COVID-19 vaccine safety report.

To date, one case of thrombosis with thrombocytopenia reported in Australia has been assessed by the Vaccine Safety Investigation Group (VSIG). The VSIG is an independent expert advisory group comprising experts in vaccine safety, public health, vaccine confidence and relevant medical specialists in blood disorders, immunology, gastroenterology, infectious diseases, convened by the TGA to assess such cases. The VSIG concluded that, based on available data, there was insufficient evidence to firmly confirm that the clot was caused by the vaccine, but emerging evidence suggests a likely association. However, this conclusion will be reviewed as further information becomes available.

The TGA is carefully reviewing all Australian reports of blood clots following the AstraZeneca vaccine, and are requesting further information from reporters where needed. Any further suspected case will be referred to the VSIG for assessment. The TGA has also been in regular contact with overseas regulators on the subject. Over the last two evenings we attended the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) meeting which discussed the risk of rare and unusual blood clotting issues in adults who have received the AstraZeneca COVID-19 vaccine. The issue was also discussed several times over the last few days by TGA with the UK Medicines and Health products Regulatory Agency (MHRA) and Joint Committee on Vaccines and Immunisation (JCVI), which advises UK health departments on immunisation.

The EMA has found that there is a possible link between the AstraZeneca COVID-19 vaccine and very rare cases of unusual types of blood clots with low platelets, with most case reports in women under 60 years of age, within 2 weeks of vaccination. Blood clots occurred in veins in the brain (cerebral venous sinus thrombosis, CVST) and abdomen and in arteries. The EMA PRAC reviewed 86 cases reported as of 22 March 2021 (62 CVST and 24 of other thromboses with thrombocytopenia), 18 of which were fatal. PRAC noted that in Europe and the UK about 25 million people had received the AstraZeneca vaccine. They stated that "the reported combination of blood clots and low blood platelets is very rare and the overall benefits of the vaccine in preventing COVID-19 outweigh the risks of side effects".

The UK regulator (MHRA) issued new advice on the afternoon of 7 April (UK time) concluding "a possible link between COVID-19 vaccine AstraZeneca and extremely rare, unlikely to occur blood clots". The MHRA reviewed 79 UK cases of thromboses accompanied by thrombocytopenia reported as of 31 March 2021 (44 CVST and 35 of other thromboses), with 51 of these case reports in women. There were 19 deaths.
MHRA reported that by 31 March 2021, 20.2 million doses of the COVID-19 Vaccine AstraZeneca had been given in the UK, meaning that the overall risk of the rare blood clots was approximately 4 people in a million who receive the vaccine. The TGA and Australian Technical Advisory Group on Immunisation (ATAGI) are continue to urgently review this information and other data as part of our enhanced safety monitoring of COVID-19 vaccines.

ATAGI met today to discuss the Europe and UK advice in the Australian context. ATAGI has recently published information about the potential risk of blood clots following immunisation with COVID-19 vaccines for consumers and health professionals. The advice includes information about symptoms that might prompt further action and how they can be managed and treated (such as seeking medical attention). This evening, ATAGI released updated advice.

The TGA encourages health professionals and consumers to report suspected side effects following immunisation with COVID-19 vaccines. Every report is valuable and contributes to our safety monitoring.

The TGA has worked with AstraZeneca to update the Product Information for the vaccine to include the latest information about the risk of very rare cases of thrombosis (blood clots) with thrombocytopenia (low blood platelet count). An updated Product Information, effective 8 April 2021 is available on the TGA website. Further updates are under consideration in light of international developments and the most recent ATAGI advice.

Further information about how to report suspected side effects to a COVID-19 vaccine is available on our website.

TGA weekly COVID vaccine safety reports

- Reports in 0.5-0.6 % of doses
- Do not equal causality, especially for special interest (serious) AEFIs

Pfizer Comirnaty vaccine:

- Most frequently reported AEFIs - Headache > Nausea > Dizziness > Fatigue > Muscle pain
- Adverse events of special interest
  - **Anaphylaxis**, Bleeding disorders, Facial weakness, Seizure, Cardiac events, Loss of taste/smell

AstraZeneca vaccine:

- Most frequently reported AEFIs - Headache > Fever > Muscle pain > Chills >Fatigue
- Adverse events of special interest
  - Thrombocytosis with thrombocytopenia
  - Anaphylaxis, Seizure, Loss of taste/ smell, Facial weakness, Joint infection

Supporting Pacific and SE Asian neighbours

- Government committed over $600m to **secure access to COVID-19 vaccines** through advance purchase agreements and the COVAX Facility
- Will help PNG, Pacific Islands and Timor Leste achieve full coverage, and a significant contribution to SE Asia
- **TGA support** to assist with assessment of vaccine safety, efficacy and quality by partner governments and strengthen local safety monitoring systems
- **TGA assistance** to support vaccine manufacture in Thailand

Vaccination is critical but does not mean we can stop taking other measures

- While being highly effective, **no COVID vaccine is 100% effective**
- **Herd immunity** won't be achieved globally for several years
- **Boosters may be required** – variants, vaccines may not provide lifelong protection
- **Effective COVID treatments will be needed** – three in use in Australia at present:
  - Corticosteroids – (patients on oxygen)
  - Remdesivir (unventilated patients)
  - Tocilizumab (immunomodulatory used in forms of arthritis) – in seriously ill patients
- But there are **not yet any 'magic bullet' antivirals for COVID-19**

Australian Government

Department of Health

Therapeutic Goods Administration