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SUBMISSION TO COMMONWEALTH GOVERNMENT COVID-19 RESPONSE INQUIRY

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AstraZeneca welcomes the opportunity to make a submission to the Commonwealth Government's independent inquiry into the COVID-19 Response.

AstraZeneca is a global biopharmaceutical company employing more than 80,000 people globally and 800 across Australia. We are one of the largest pharmaceutical manufacturers in Australia and have been manufacturing at our facility in North Ryde, Sydney, for over 50 years.

Recognising the urgent need for the medical community to work together to research a vaccine to defeat the virus, AstraZeneca joined forces with the University of Oxford in April 2020, to rapidly develop and supply a COVID-19 vaccine (later known as the Oxford/AstraZeneca Vaccine, COVID-19 Vaccine AstraZeneca, or Vaxzevria™ (ChAdOx1-S)). AstraZeneca supplied over three billion doses of this vaccine to more than 180 countries, and approximately two-thirds of these doses were delivered to low- and lower-middle income countries. This vaccine was provided on a global no-profit basis during the pandemic period.

The Oxford/AstraZeneca Vaccine is estimated to have saved more than 6.3 million lives worldwide in the first year of its availability[1]. One in three Australian adults received the Oxford/AstraZeneca Vaccine, equating to 13.8 million doses, the majority of which were manufactured locally in partnership with CSL.

AstraZeneca also quickly mobilised research efforts to develop a coronavirus-neutralising monoclonal antibody combination called Evusheld™ (tixagevimab and cilgavimab), for the prevention and treatment of COVID-19. Evusheld™ was provisionally approved by the Therapeutic Goods Administration (TGA) in February 2022 for the prevention of COVID-19 in people not expected to mount an adequate immune response to vaccination because they are immunocompromised due to a medical condition or due to immunosuppressive medications. 39,000 doses were delivered through an Advance Purchase Agreement (APA) with the Department of Health and Aged Care and distributed via the National Medical Stockpile (NMS), providing additional protection to vulnerable Australians.

AstraZeneca has identified four key recommendations for consideration by the Panel that would improve Australia's future pandemic preparedness:

1. Establish a National Medical Manufacturing Taskforce to enhance Australia's domestic medical manufacturing capability and reduce the impact of future supply chain disruptions.

[1] Chuenkitmongkol S et al. Expert review on global real-world vaccine effectiveness against SARS-CoV-2. Available at: https://doi.org/10.1080/14760584.2022.2092472

2. Provide alternative funding pathways for preventative therapies and improve national distribution channels for medicines funded outside of the Pharmaceutical Benefits Scheme (PBS).
3. Improve pandemic communications by allowing pharmaceutical companies to publicly respond to public concerns in a factual and balanced manner, when in the national interest.
4. Establish ongoing monitoring of COVID-19 mutations and circulating variants of concern.

RECOMMENDATION 1

Establish a National Medical Manufacturing Taskforce to enhance Australia's domestic medical manufacturing capability and reduce the impact of future supply chain disruptions.

The COVID-19 pandemic saw major disruptions to global supply chains, resulting in shortages in pharmaceuticals and essential medical equipment such as Personal Protective Equipment (PPE). Establishing the priorities for domestic medical manufacturing through the establishment of a National Medical Manufacturing Taskforce would ensure Australia can plan for and secure critical supplies in the future, as well as enhancing Australia's global bargaining power during future supply chain disruptions.

While medicine shortages are not new to Australia, the COVID-19 pandemic highlighted many of the fragilities of Australian supply chains, particularly for medicines. Shortages for vital medicines were experienced throughout the pandemic, including for medicines used to manage asthma, diabetes, depression, anxiety and nausea, as well as treatments for stroke, hormone replacement, antibiotics, cancer treatments, and liquid paracetamol.

There are two main stages of pharmaceutical manufacturing – production of active pharmaceutical ingredients (APIs), and the production of formulations (medicines, whether in cream, tablet, capsule, inhaler, or other forms). According to the TGA, Australia imports over 90% of medicines, primarily from the US and Europe, whilst most APIs are manufactured in China and India.

Shortages were the result of multiple factors including disruptions to supply chains, as well as panic-buying and stockpiling in Australia and around the world. In some cases, access to APIs was limited, production at international manufacturing plants was impacted by workforce shortages resulting from the pandemic, and air and sea freight was disrupted.

One such example of these supply constraints was seen in March 2021 when the European Union blocked a shipment of the Oxford/AstraZeneca Vaccine bound for Australia. In efforts to secure domestic supply, the European Union refused to authorise a shipment of 250,000 vaccine doses from AstraZeneca's Italian manufacturing facility to Australia. The European Union justified this decision as Australia was not considered "vulnerable" due to the low number of COVID-19 cases in Australia at the time.

In April 2021, the Australian Government sourced an additional 717,000 vaccine doses from the United Kingdom, to make up for the shortfall in doses blocked by the European Union. While nearly 4 million doses of the vaccine were ordered offshore, AstraZeneca and the Australian Government entered into a partnership with CSL to ensure that the vast majority – almost 50 million doses – would be manufactured locally in Australia. This safeguarded AstraZeneca's vaccine supply from global supply chain disruptions.

The TGA took action to manage medicine shortages during the pandemic by establishing the Medicine Shortages Working Party. While the Government has now implemented stockholding requirements to help address global supply chain issues, this should not be viewed as a long-term

solution to manage supply disruptions of more than 4-6 months. Australia remains reliant on offshore manufactured product. Global health crises, trade disputes, political disputes, labour shortages or civil unrest will all continue to cause shortages of critical medicines in the future.

Recently, we've seen Australian supply chains disrupted once again, this time due to a cyber-attack on DC World, who is responsible for 40% of Australia's maritime freight. With cyber-attacks becoming more frequent, this is another important consideration for government when setting manufacturing policy.

A nationwide assessment conducted by a National Medical Manufacturing Taskforce would allow the Government to determine a list of medicines deemed "critical" for the day to day functioning of our health system – medicines people use at home, those most commonly used in primary healthcare settings, and those used in hospitals. This would differ to the function and purpose of the NMS, which plans for specific events (such as a pandemic). The Taskforce would help inform manufacturing policy and determine key areas for future government investment in sovereign capability.

RECOMMENDATION 2

Provide alternative funding pathways for preventative therapies and improve national distribution channels for medicines funded outside of the PBS.

Existing Australian Technical Advisory Group on Immunisation (ATAGI) and Pharmaceutical Benefits Advisory Committee (PBAC) processes are not structured as funding pathways for therapies authorised for pre-exposure prophylaxis of COVID-19, and the length of the PBS decision-making process does not support rapid access to critical medicines during a pandemic. NMS distribution of medicines funded through other channels, such as APAs, can be challenging without the vast distribution network of the PBS. Alternative funding pathways outside of emergency settings are crucial to ensuring vulnerable Australians have equitable access to protection.

Despite the high effectiveness of COVID-19 vaccines, some immunocompromised patients are unable to develop an immune response and remain at risk of life-threatening infection.

Whilst approximately 3% of the Australia population are immunocompromised (approximately 500,000 people), data from the "Communicable Diseases Intelligence COVID-19 Australia: Epidemiology Reports"[2] indicate that they account for up to 25% of hospitalisations or ICU admissions for COVID-19. Studies in the UK[3] and USA[4] have also demonstrated similar data with immunocompromised patients accounting for 3.7% of the UK population, yet being overrepresented in hospitalisations (20%), ICU admissions (28%) and deaths (24%) due to COVID-19.

As highlighted by ATAGI, "studies also show that the immunocompromised population with COVID-19 have a 1.5-2.0 times higher risk of death than the general population. In addition, prolonged COVID-19 infection, which immunocompromised individuals are more susceptible to, is associated

[2]health.gov.au/internet/main/publishing.nsf/Content/99424DA2A5F3A488CA2589BA0019141B/$File/covid_19_australia_epidemiology_report_78__reporting_period_ending_27_august_2023.pdf

[3]Evans RA et al. In press-corrected proof. *Lancet Reg Health Eur*. 2023. https://doi.org/10.1016/j.lanepe.2023.100747.

[4] Ketkar A et al. *Curr Med Res Opin*. 2023;39(8):1103-1118

with prolonged viral shedding, which increases the risk of viral evolution and of the development of new viral variants"[5].

Evusheld™ was developed to meet significant unmet need and provide an additional layer of protection for these patients. Clinical trials and real-world evidence supported the effectiveness of Evusheld™ to protect these high-risk individuals. Evusheld™ is the only monoclonal antibody (or antibody combination) authorised for pre-exposure prophylaxis in Australia.

Following TGA registration in February 2022, Australia's National COVID-19 Clinical Evidence Taskforce (CET) and state and territory-based guidelines recommended Evusheld™ for pre-exposure prophylaxis therapy for immunocompromised patients in March 2022. The National COVID-19 CET also recommended Evusheld™ for treatment of COVID-19.

AstraZeneca worked closely with the Department of Health to prepare an abridged submission for Evusheld™ as part of an application for PBS listing. Evusheld™ was rejected at the December 2022 PBAC meeting.

While Australia's PBS listing process is robust, it is a widely held view that it is too restrictive for the emergency assessment of therapies. The National Health Act requires PBAC to be satisfied that cost-effectiveness has been established before a medicine can be recommended for listing on the PBS. This regulation requires a high level of certainty in both the clinical utility and utilisation of the therapeutic intervention. This process does not therefore allow for the agility in decision making that is necessary to support short term PBS listings of therapies in situations with a high degree of uncertainty, such as the constantly evolving COVID-19 environment.

An APA was signed between AstraZeneca and the Government in December 2021 and then varied in February 2022, and 39,000 doses of Evusheld™ were supplied to be distributed via the NMS. Supply to states and territories via the NMS was challenging and resulted in inequitable access to Evusheld™ for immunocompromised Australians.

State and territory guidelines for Evusheld use were not consistent nationally, and changed from time to time causing confusion about who should receive the drug. Therefore, the requirements to demonstrate eligibility differed across states, with some states requiring copious amounts of paperwork and serology. Many hospitals did not have the resources to search their records for, and recall, eligible patients, and there was no additional funding to support this cost, or to support additional costs such as storage or transport to regional and remote areas. In some instances, states were also known to be stockpiling Evusheld™ due to uncertainty about future availability and supply arrangements.

Overall, this distribution approach resulted in slow uptake of Evusheld™, low awareness, and low levels of familiarisation, resulting in fewer immunocompromised Australians receiving protection.

AstraZeneca maintained engagement with the states and with Patient Advocacy Groups to ensure awareness of supply arrangements, to understand utilisation rates for forward planning, and to ensure understanding of Evusheld™ neutralisation against emerging variants of concern.

[5] ATAGI. 2023. "Recommendations on the use of a 3rd primary dose of COVID-19 vaccine in individuals who are severely immunocompromised" Version 4.3 5.

The Halton Review of COVID-19 Vaccine and Treatment Purchasing and Procurement [6](the Halton Review) concluded that over the next two years, Australia must continue to ensure that there is adequate and speedy access to vaccines and treatments by patients, if and when they are required; and that maximum possible protection through vaccinations and treatments should be provided over the short to medium term to protect the vulnerable, limit hospitalisation and death, and allow the economy and health system to recover.

The Halton Review also found that pre-pandemic structures and processes were not fit for purpose in an emergency context, and that ongoing, integrated advice and new advisory structures and mandates will be required for the ongoing management of COVID-19. It found that the potential benefit of wider use of efficacious treatments should be considered, given the considerable ongoing disruption to work and education still being experienced.

The flexibility and adaptability shown by the Government in an emergency setting was crucial to allow APAs to be agreed in a rapidly changing environment. To improve Australia's future pandemic preparedness, consideration must be given to providing appropriate and flexible funding pathways for pre-exposure prophylaxis therapies and improving distribution of medicines funded through alternative pathways outside of the PBS.

RECOMMENDATION 3

Improve pandemic communications by allowing pharmaceutical companies to publicly respond to public concerns in a factual and balanced manner, when in the national interest.

The rollout of the COVID-19 Vaccine AstraZeneca was impacted by public misperception relating to the risks associated with the vaccine. In preventing pharmaceutical companies from promoting medicines, TGA regulations inadvertently prevented AstraZeneca from proactively responding to incorrect claims associated with adverse events. Pandemic arrangements should be considered by the Panel, to prevent such situations arising in the future.

Recognising the urgent need for a vaccine to defeat the virus, in April 2020 AstraZeneca joined forces with the University of Oxford to rapidly develop and supply a COVID-19 vaccine. In February 2021, COVID-19 Vaccine AstraZeneca was provisionally registered by the TGA for individuals aged 18 years and above. The vaccine was first made available to Australians in March 2021.

On 8 April, ATAGI issued advice that due to a rare but potentially severe side effect linked to the COVID-19 Vaccine AstraZeneca, it was no longer the preferred vaccine for 16–50-year-olds, while there were very few COVID-19 cases in the community. ATAGI advised that in an outbreak, either vaccine was likely to be beneficial, and if the Pfizer vaccine was unavailable, it was preferable for people under 50 to receive the AstraZeneca vaccine, however they should consult their doctor.

On 17 April, the Department of Health paused advertising on the vaccine rollout. On 4 May, the Australian Government recalibrated its rollout strategy to utilise doses of the COVID-19 Vaccine AstraZeneca by bringing forward eligibility for 50+ Australians. On 17 June, ATAGI advised that the COVID-19 Vaccine AstraZeneca was no longer the preferred vaccine for 50–59-year-olds. The COVID-19 Vaccine AstraZeneca remained registered by the TGA for individuals aged 18+.

The nuances in ATAGI's advice were quickly lost amongst the media and public commentators, with many interpreting the advice to say that there was a prohibition on the use of the AstraZeneca

[6] https://www.health.gov.au/resources/publications/review-of-covid-19-vaccine-and-treatment-purchasing-and-procurement-summary-and-recommendations

vaccine for persons under 50, and then under 60, rather than a recommendation. The risk/benefit analysis of receiving the vaccine, and any COVID-19 vaccine, was not well understood by politicians, the mainstream media, or the general public. Media reporting resulted in public confusion regarding vaccine eligibility and led to vaccine hesitancy amongst members of the public.

At the time, TGA regulations made it difficult for AstraZeneca to publicly respond to media reports regarding adverse events and risks associated with the vaccine for the population groups which ATAGI recommended should receive the vaccine. Throughout this period, AstraZeneca responded to direct media enquiries.

Confusion was partially the result of media and the public not sufficiently understanding that ATAGI acts in an advisory capacity. It's not uncommon for there to be differences in clinical opinion between different clinical groups, such as between ATAGI and PBAC.

The Halton Review concluded that to maximise coverage and reduce confusion, it is important for government to clarify who the key decision-maker on vaccine eligibility is and which bodies act in an advisory capacity. This Review also concluded that public messaging needs to be better aligned with public health goals, and high-level COVID-19 vaccine policy.

Pandemic arrangements should be considered under TGA regulations, that would allow pharmaceutical companies to publicly respond to such concerns in a factual and balanced manner when in the national interest, to prevent such situations from arising in the future.

RECOMMENDATION 4

Establish ongoing monitoring of COVID-19 mutations and circulating variants of concern.

At present, data collection and monitoring in Australia is fragmented and intermittent, making data unreliable and unapplicable to the Australian population as a whole. Establishing ongoing monitoring of COVID-19 variants would help inform decisions on the role and funding of therapies to prevent and treat COVID-19.

The development and ongoing global rollout of COVID-19 vaccines was made possible through post approval real world data (RWD) collection and studies. These insights reflect daily interactions with the healthcare system for millions of people, including those often excluded from randomised controlled trials (RCTs).

It is essential that Australia collects its own data to continue to monitor COVID-19 mutations and circulating variants of concern, as countries continue to experience different variant waves at different times. This means information collected overseas data may only be partially applicable to Australia.

The Halton Review recommended ongoing monitoring of COVID-19 mutations and variants, including impacts on treatment efficacy. Collecting and reporting on such data would also sustain public awareness of the risks associated with COVID-19, encouraging greater uptake of vaccine boosters and other options for the prevention and treatment of COVID-19.

We recommend establishing a linked framework for Australian governments to collect data, with wastewater surveillance as the backbone of this framework, accompanied by targeted genomic sequencing of variants of interest. This would enable an evidence-based approach for Australia's ongoing diagnosis, management and treatment of COVID-19.