GMP FORUM 2023

Welcome and opening remarks
The regulatory landscape – with an eye to manufacturing issues

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Overview

Manufacturing quality central to all medicine and vaccine products

- *TGA GMP and clearance statistics*
- *What did we learn from the pandemic*
- *Evolution of GMP reliance*
- *Some current GMP issues – nitrosamines, medicinal cannabis, comp meds, sunscreens, MRNA products*
- *What else is happening in medicines and vaccines at the TGA ?*
- *Medicine shortages and manufacturing issues*
- *Cells and tissues, faecal transplants, leeches and maggots*
- *TGA's public good role has significantly increased*

Outcomes of inspections of Australian manufacturers

As at 30 June 2022, there were 265 Australian companies holding manufacturing licences covering 410 sites

	2020-21	2021-22
	Number (% of Total)	
Compliance status (Australia)		
Number of inspections conducted	210	139
Satisfactory compliance (of completed inspections)	139 (66%)	99 (71%)
Marginal compliance (of completed inspections)	35 (17%)	25 (18%)
Unacceptable (of completed inspections)	9 (4%)	7 (5%)
Compliance under assessment	27 (13%)	8 (5%)

Foreign inspection statistics 2021/22

	2020-21	2021-22
	Number (% of Total)	
Number of inspections conducted	54	104
Satisfactory compliance	41 (76%)	80 (77%)
Marginal compliance	4 (7%)	17 (16%)
Unacceptable	1 (2%)	2 (2%)
Compliance under assessment	8 (15%)	5 (0%)

GMP clearances 2021/22

	2020-21	2021-22
	Number (% of Total completed)	
Approved	6,778 (93%)	8,103 (91%)
Rejected	524 (7%)	799 (9%)
Total completed	7,302 (100%)	8,902 (100%)

The importance of vaccine GMP during the pandemic

Need for rapid expansion of global manufacturing capacity presented 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 helped mitigate many of these risks

The COVID-19 GMP hangover

GMP Inspections:

- Years of international travel restrictions have resulted in a large numbers of manufacturers requiring inspections, affecting all regulators
- Manufacturers blame COVID-19 when poor GMP compliance identified

GMP Clearance:

- Flexibilities introduced during the pandemic increased the complexity and risk profile
- Application volumes and work on hand continue to increase
- Target timeframes increased

Remote and hybrid audits - benefits and challenges

Remote audits = Performed offsite in real time with the audited party using videotelephony

Hybrid audits = One auditor on site for at least part of the audit PLUS remote audit component

Benefits

- Increased efficiency – more audit days, fewer days and costs lost to travel
- Can bring in wider range of technical expertise
- Ability to audit in high-risk travel areas

Challenges

- May not be as effective – hard to review all manufacturing activities, and paper records, detect nonconformities
- Can be seen as confrontational, language issues, time zone differences, Internet patchy
- Audits can take more time

Can the GMP inspection reliance model evolve ?

Australia has one of the most extensive reliance models

For **overseas manufacturing sites**, TGA either performs:

- A desktop audit of the overseas site incorporating evidence from “Recognised Regulatory Authorities” (RRA), OR
- An inspection of the overseas site

The **extent to which we rely on inspection outcomes from the RRA** is dependent on

- Level of equivalence between TGA and the RRA (not all PIC/S members are equivalent)
- International agreements (e.g. MRAs) and other arrangements in place

But the TGA needs to

- Better document rationale for acceptance of RRA GMP inspections and have a transparent framework for assessing new and existing partners
- Determine whether third country inspections by RRAs can be in scope for GMP Clearances
- We plan to develop and communicate a “GMP Inspection Reliance Framework” in 2023-24

Nitrosamine contamination of medicines

- **Nitrosamine contamination** found in a number of medicines since 2018 globally
  - Sartans, ranitidine, metformin, varenicline, rifampicin, quinapril, sitagliptin, reboxetine
- **Levels are small however**
  - If a patient takes the medicine for 70 years should not increase cancer risk by more than 1 in 100,000 based on animal studies
- Generated **during manufacturing or storage**
  - US FDA working with manufacturers on process changes to determine whether contamination can be reduced

Medicinal cannabis GMP reforms

Current situation

- All medicinal cannabis products supplied in Australia must comply with a product standard TGO 93
- Australian manufacturers of medicinal cannabis products must hold a TGA GMP manufacturing licence
- There is an exemption from holding GMP evidence for starting materials only if it is further manufactured at a GMP approved facility
- Compounding of medicinal cannabis products still permitted but SAS or AP approvals now required before prescribing

After 1 July 2023

- Importers of medicinal cannabis products will have to be “manufactured to a recognised international GMP standard”
- Levels playing field – list of GMP standards on the TGA website

GMP for complementary medicines and sunscreens

GMP inspections required because Australian law classifies both as medicines

Sunscreens

- TGA guidance for demonstrating compliance with PIC/S
- New evaluation pathways for sunscreen actives and excipients
  - Mandatory requirements for new ingredient applications, but data requirements tailored for products for topical use
  - Mandatory review timeframes and appeal rights for ingredient applications
  - Use of monographs for certain ingredients
  - New sunscreen standard addresses application methods for spray sunscreens

Complementary medicines

- Reinspection frequency based on risk
- Yet some compliance concerns with certain manufacturers

mRNA vaccines and therapeutics – additional GMP issues

Quality and consistency of the lipid nanoparticles as important as mRNA

mRNA vaccines - encoding a viral protein to elicit a protective immune response for prophylaxis of viral diseases and immunotherapies for cancer

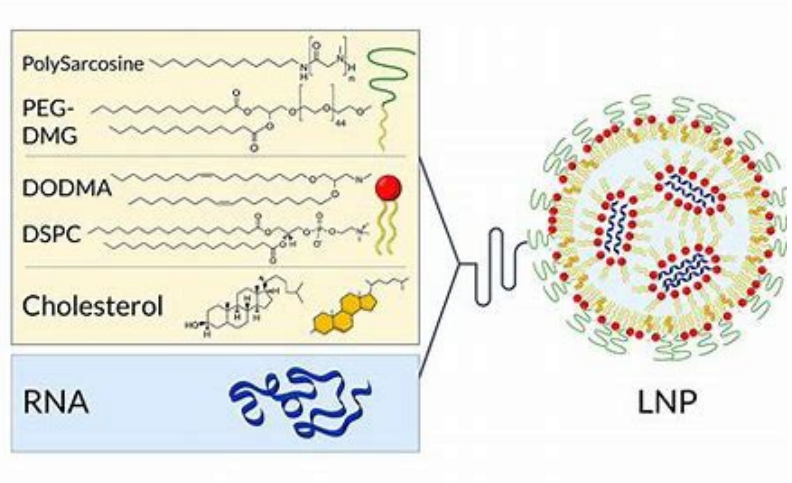
mRNA therapeutics – for treatment, mitigation or cure of a disease - encoding a protein that is missing or dysfunctional in the patient to provide functional gene expression

Manufacture of the stabilising and delivery system of the mRNA (usually lipid nanoparticles) requires close review as part of drug product manufacturing

Raw material lipids should also be carefully controlled

For the drug product, **determine consistency of manufacture:**

- quantify the amount of mRNA encapsulated
- determine the size distribution of particles



mRNA vaccines and therapeutics

Major process points for quality control

Manufacturing controls

- Validation of all processes for consistency and product stability - manufacturer needs to agree release specification and product characterisation methods with regulator
- Control of starting and raw materials
- In-process control of the manufacturing process critical – bulk mRNA, LNP manufacture, encapsulation as is characterisation of the drug substance and final filled vaccine (drug product)

Stability testing

- Storage temperature and expiry date based on real-time evidence - consider shelf-life extensions later
- Must be in the final vials used commercially
- Short term stability at refrigerator and room temperatures also important to inform clinical deployment
- Stability and freedom from microbial contamination particularly important for multidose vials

What else is happening in medicines and vaccines at the TGA ?

Facilitated prescription medicine pathways enable earlier patient access

But they can put pressure on GMP inspection or clearance requirements

Priority review (max 150 working days)

- 48 have been approved under this pathway since July 2017
- Average decision time 126 working days

Provisional Approval

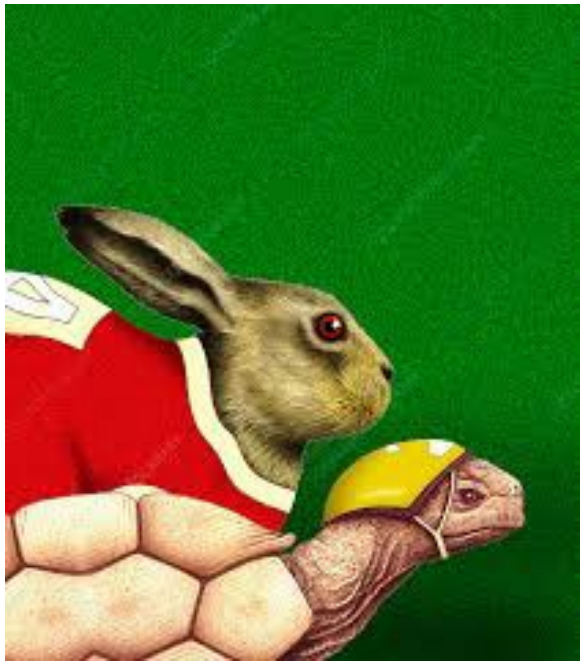
- 60 have been approved since 2018
- Average decision time 70 working days

Comparable Overseas Regulator pathway

- 58 approved since 2018

ACCESS Worksharing initiative

- 25 NCEs and 8 generics approved since 2018



Generic medicines reforms

Only some relate to manufacturing quality, although it is important to ask sponsors to maintain up to date manufacturing site information

- Requirement to include **Product Information hard copy in injectables** being reviewed
- Developing guidance for **supplying prescription medicines in shortage** that do not have Australian specific labelling
- **Early scientific advice** – complex generics, possibly also non-oral dose forms
- Greater **use of overseas reference products for bioequivalence**
- **Complex generic products** – review regulatory pathways, strengthen international cooperation
- **Reforms to application and evaluation processes** – submission of additional data, updating of Product Information

On the other hand, a period of consolidation following many recent complementary medicine reforms

- **Permitted indications**
- **Efficacy evidence guidelines**
- **Listed (Assessed) pathway** - data protection and efficacy claimers
- **Permitted ingredients** (and an online catalogue)
- **Sport supplement reforms**
- **Market exclusivity** for new ingredients
- More comprehensive **post-market monitoring**
- **Compliance review database**
- **Risk-based GMP reinspection frequencies**

Paracetamol and Psychedelic rescheduling – 3 February 2023

Paracetamol – interim decision

Responsive to increasing incidence of intentional self-poisoning - about 50 deaths per year and 250 serious liver injuries

- Reduce size of packs on general sale from 20 to 16 tablets/capsules and require blister packs
- Reduce size of pharmacy only (S2) packs to 32 tablets/capsules and require blister packs
- Other packs of up to 100 tablets/capsules

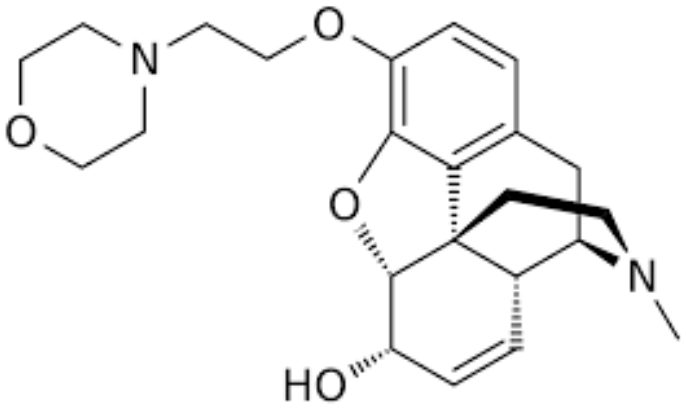
Psychedelics – final decision

Rescheduling to Schedule 8 (“controlled drugs”) of **psilocybin for treatment-resistant depression**, and **MDMA for post-traumatic stress disorder**

- Authorisation to prescribe the substances for the above conditions restricted to registered psychiatrists who have obtained **approval from a Human Research Ethics Committee** and have also been authorised by the **TGA to be an Authorised Prescriber**
- TGA Advice on **local manufacturing requirements** for psilocybin mushrooms to come soon

Pholcodine cancellation and recall

- Pholcodine was used widely in **OTC cough syrups and lozenges**
- Shown to cause a **significantly increased risk of serious anaphylaxis** if neuromuscular blocking agents are used in anaesthesia
- **Recalled at pharmacy level** effective 8 March and **cancelled from ARTG** effective 29 March 2023
- **Main alternative product** is dextromethorphan
- **May require GMP inspections / clearances** of new dextromethorphan API and finished product facilities



Medicine shortages – manufacturing issues are often at the centre

- **Often older, low profit generics** with only 1-2 API manufacturers globally
- **Currently 40-50 critical medicine shortages** – shortages of antibiotics, diabetes, warfarin, steroid medicines high profile
- Some other medicines in shortage **difficult to manufacture** so rapid scale up not possible
- **TGA actions**
  - Bring sponsors, wholesalers and healthcare professionals together - managing supply
  - Approve temporary supply of overseas substitutes
  - Allow pharmacists to dispense substitute combinations of different strengths
  - Wholesalers to facilitate equitable distribution
  - Public and prescriber communications

Renewed interest in domestic manufacturing

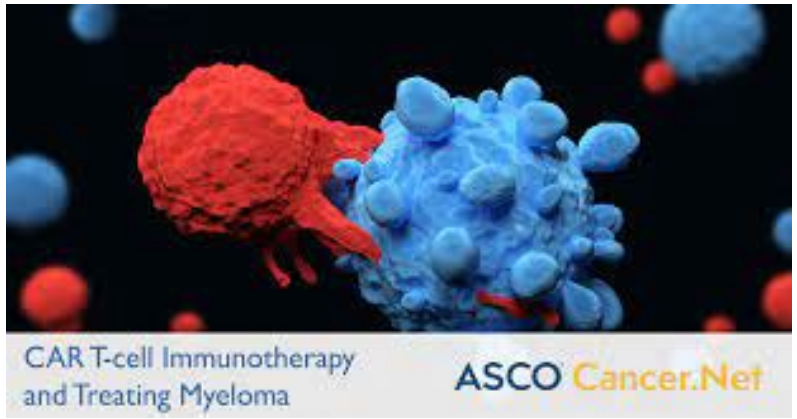
- **Commonwealth and State/Territory funding** of initiatives
- **Not easy for existing manufacturers** to pivot to new products
- **Some medicines are very complex** and difficult to step up manufacture of
- **Australian market may not be sufficient** for Return on Investment for local manufacture – so local manufacturers will need a regulatory strategy to support export
- **TGA will be ready to support the companies** as needed – as we did during COVID

$15 billion National Reconstruction Fund – announced in Oct 2022 budget

To diversify and transform Australia's industry and economy and drive sustainable economic growth

- **“Medical science” one of 7 priorities** - including supporting essential supplies
- **Government has earmarked $1.5 billion** investment in medical manufacturing
- Other areas include
  - renewables and low emissions technologies; transport
  - value-add in the agriculture, forestry and fisheries sectors; value-add in resources
  - defence capability; enabling capabilities
- **It will provide finance** (including loans, guarantees and equity) to drive investments and look for co-investment to add value and develop capability
- **NRF will operate commercially** and its board will make independent investment decisions

Essential supplies vs industry transformation ?



Australian Medtech Manufacturing Centre

$ 20 m Victorian Government initiative aims to:

- **Grow medtech manufacturing** in Victoria
  - Mapping capability in supply chain and local procurement opportunities
- **Increase local content in procurement** of health products
  - Grants to local companies for medtech manufacturing
  - Clinical researcher – medtech partnerships
- **Improve collaboration** between government, indudtry and health sectors
  - In medtech, cell and gene therapies, medical software

Cell and tissue manufacturing

GMP quality and scale up an increasing issue

Especially an issue for clinical trials – scale up from clinical trial scale to commercial scale can be challenging

Autologous human cell and tissue (stem cell) reforms 2018

- Non-minimally manipulated products and products for non-homologous use now within TGA regulatory framework
- CART cells pose particular challenges as cells collected and infused locally but processed offshore – class 4 biologicals
- Three products approved – Kymriah, Yescarta, Tecartus – certain leukaemia and lymphomas

TGA regulation of faecal microbial transplants

- **First regulatory approval globally** was by TGA
  - Currently approved only for treatment of *Clostridioides difficile* infection - trials underway for use in other conditions
- **New faecal microbial transplant regulatory framework** commenced on 1 July 2021
  - Commercial products are class 2 biologicals and require GMP, TGA review and ARTG registration
  - In-house hospital products are class 1 biologicals with lower regulatory oversight
- **Medical and leeches and maggots** will be next, and commercial provision will require GMP
  - Regulated differently overseas – medicines (Canada, EU) versus medical devices (US)

TGA's public good role has significantly increased - 1

Many activities cannot be directly attributed to a particular sponsor or may not be appropriate to cost recover

- **Orphan drug scheme** for rare diseases and less common cancers – 28 designations /yr
- 222,000 **Special Access Scheme** and 14,000 **Authorised Prescriber Scheme** approvals for patient access to unapproved products where registered ones have not succeed
- **Management of Medicines shortages** – 12,000 reports annually
- **Emergency access to products**

TGA's public good role has significantly increased - 2

- **Compliance and enforcement** – 33,000 investigations annually
- Access to prescription **medicinal cannabis** and **nicotine vaping products**
- **Responding to enquiries** – 87,500 phone calls and emails annually
- **Assistance to small business and research developers of emerging therapies and devices** – 60,000 enquiries /yr
- **Public communication and education** – 20 million reaches on social media/yr

So finally, we do have teeth – but we will not be reckless

- **TGA's Compliance and Enforcement Powers** were significantly increased following Act changes in 2018
- **Graded range of powers** – warning, enforceable undertaking, fines, civil and criminal action
- **Infringement notices** are a rapid and effective tool
  - If issued to a company they are named in the media
  - Recipient is entitled to dispute the notice
- **TGA has issued $ 3.82 m in fines** in last 19 months (we don't get to keep the money !)
  - Mainly for alleged advertising and import breaches
  - But $ 100 k in fines were issued to companies for products allegedly not conforming to applicable standards or failing to observe manufacturing principles

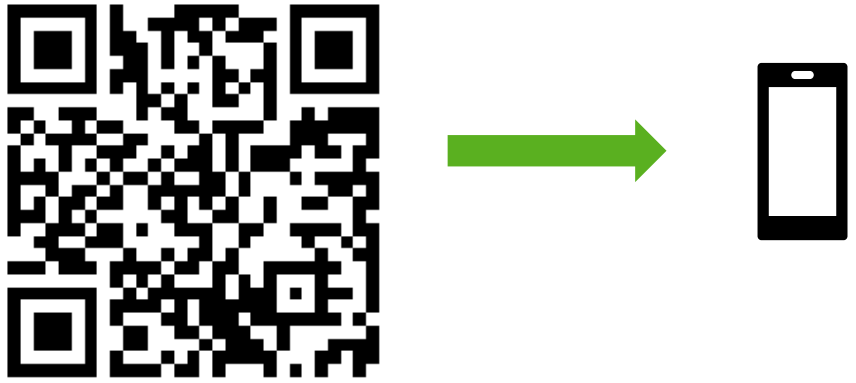
Participate in the Q&A

Verbal questions:

Raise your hand to ask a verbal question. A member of the GMP Forum staff will provide a roaming microphone.

Written questions:

Scan the QR code below or click the link in your calendar to access Slido via your mobile device. You can submit your question, and vote on other questions submitted.



Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration