Australian Government
Department of Health
Therapeutic Goods Administration

Updates from the Therapeutic Goods Administration

Early access to medicines schemes: Local perspective

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International Society of Pharmacovigilance
Training Course: March 15th- 18th 2018

Presentation Overview

- Overview of Australian expedited pathways
  - Priority review pathway
  - Provisional approval
- Considerations for Implementation in Australia
- Other options for access to medicines

TGA expedited pathways

- To facilitate earlier access to medicines that address unmet clinical needs for Australians, without compromising standards for safety, efficacy and quality.
- Two new 'expedited' pathways for prescription medicines based on the government response to the recommendations of the MMDR review:
  - **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances

    Implemented 1 July 2017
  - **Provisional Approval** on the basis of early data on safety and efficacy, where the immediate availability of the medicine outweighs the risk that more data is required

    Likely to be implemented in the next few days

Determination process

- To use the pathways, a determination must be obtained before lodging a submission – “Entry ticket”
- Formal process to assess against the eligibility criteria
- Determinations lapse after 6 months
  - 1 extension possible for provisional, Priority cannot be extended
  - Positive determination decisions are published on the TGA website (https://www.tga.gov.au/designation-notices)
- Ineligible determination decisions are appealable by the sponsor only

Why determine?

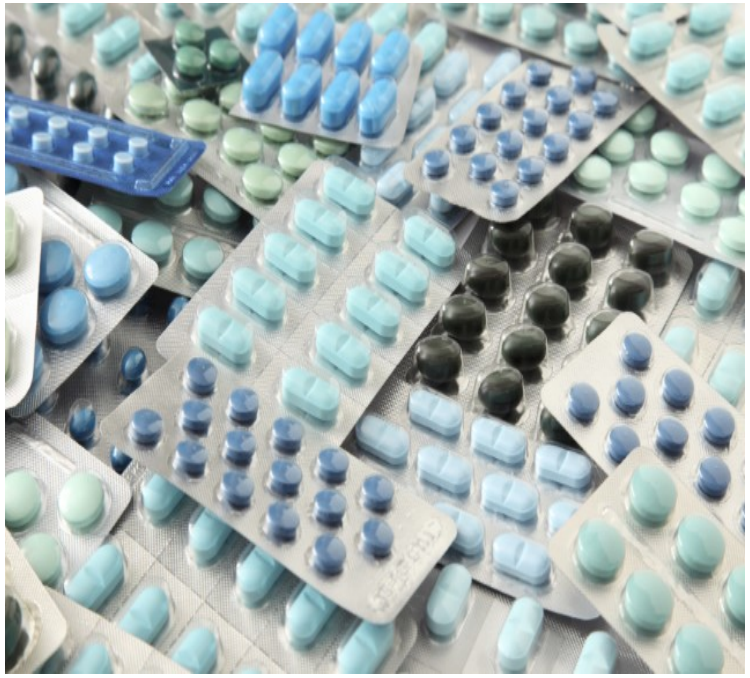
- Early look at the data – Early assessment of benefit-risk (before the registration application is received)
- Gives certainty of applications to both Sponsor and TGA
- Avoids outright rejection of indication/registration sought
- Estimation of future work load
  - 7 /10 priority determinations are for anticancer medicines
- Allows us to see if we have criteria right for public health reasons
- Consistent and transparent process for assessing eligible medicines

Determination Eligibility criteria

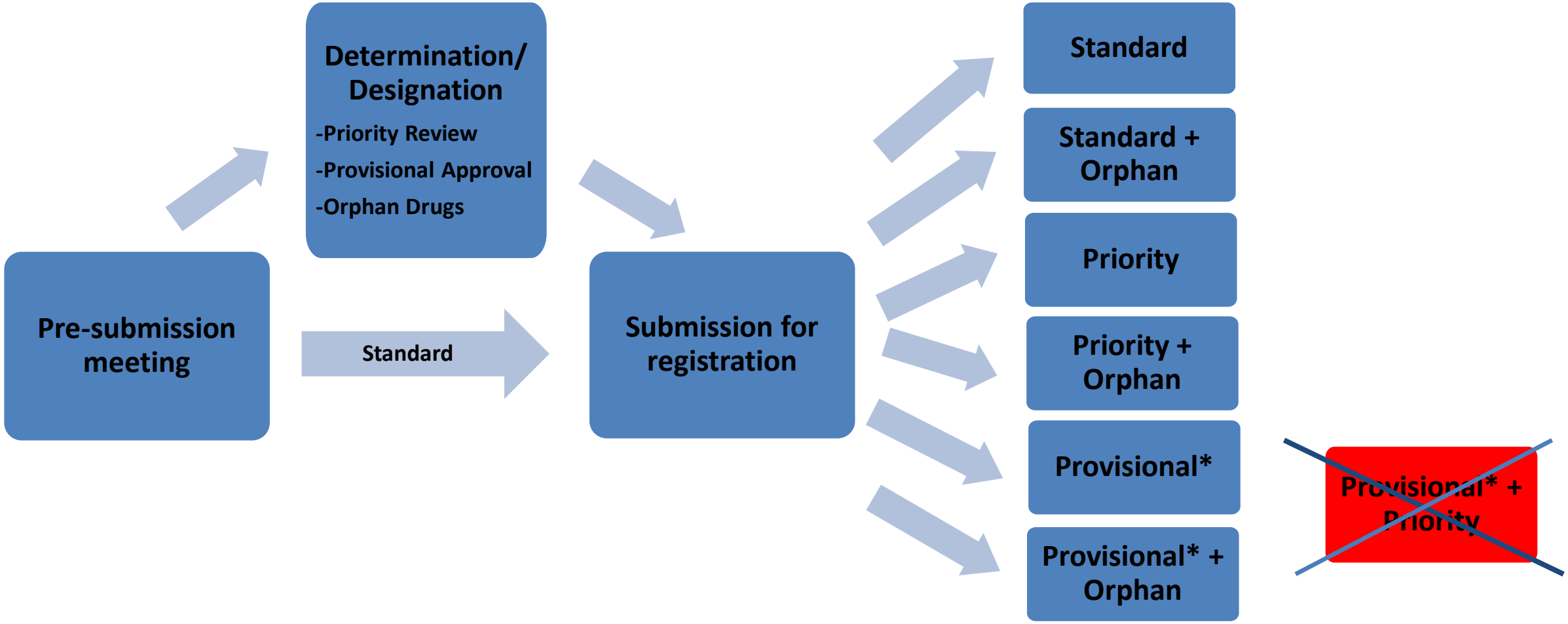
Criterion	Provisional	Priority
New prescription or new indications medicine	Yes	Yes
Serious or life-threatening condition	Yes	Yes
Comparison against registered therapeutic goods (*excludes provisional registration)*	Yes – **data preliminary**	Yes **– data substantial**
Major therapeutic advance	Yes**– data preliminary**	Yes**– data substantial**
Clinical study plan	Yes	No

Determination administrative requirements

- Must use eCTD format
  - Manage increased number of simultaneous applications
  - PI and CMI changes may be required – impact on other areas
- For priority – resolve GMP early



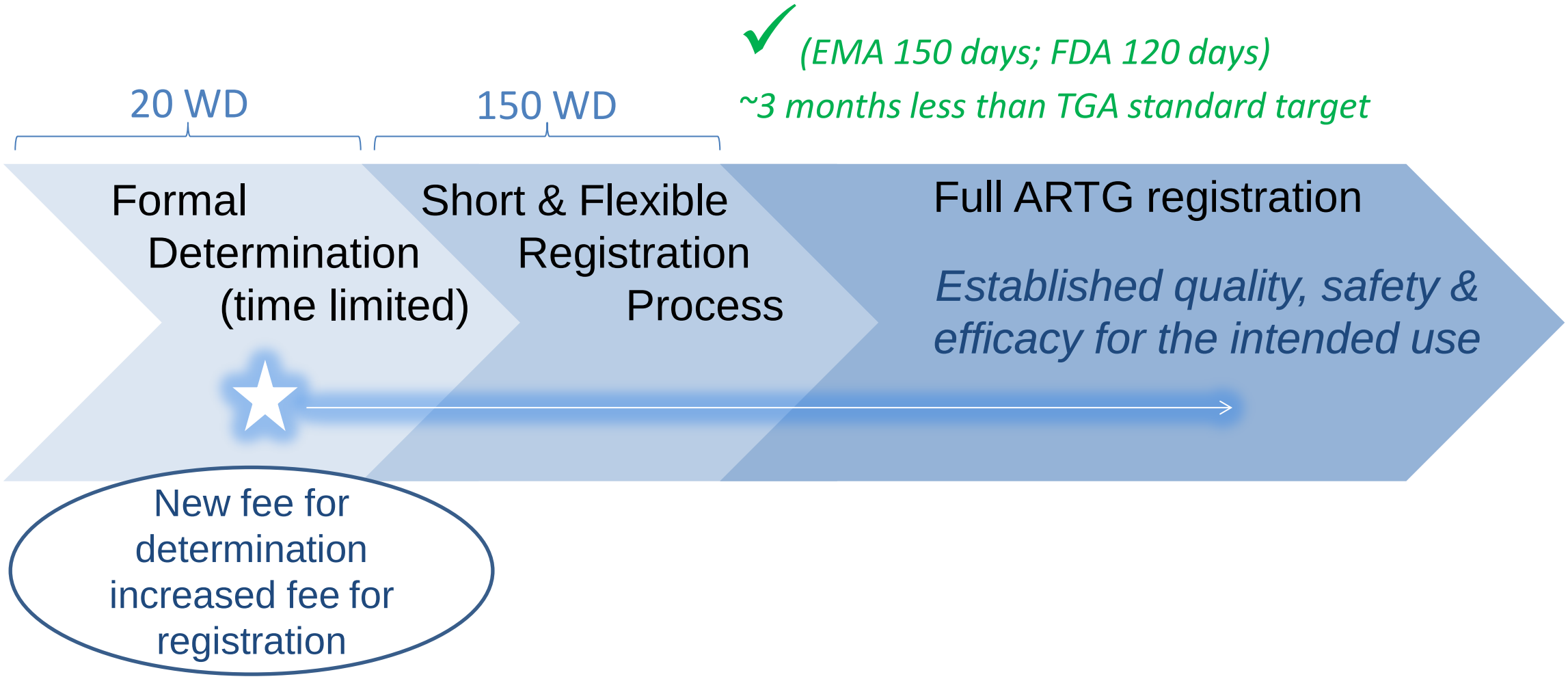
Pre-submission and submission process



Priority Review Process

✓ *(EMA 150 days; FDA 120 days)*

~3 months less than TGA standard target



How do we consistently meet timelines?

- Flexible business processes to reduce the subsequent registration timeframe
- ‘Partnership’ with applicant, standard timeframes will apply if requirements for Priority Review are not met
- The first and second round evaluation phases can be condensed
- Rolling questions during the first round assessment process
  - Provides speed and re-assurance for the clinical evaluation
  - Gives an indication of emerging issues
- Flexible arrangements for seeking expert advice

Provisional approval

- Intended to strike a balance between making decisions on the basis of promising data for the benefit of Australian patients, knowing that we need to proactively manage the risks of more unknowns about the efficacy and safety of these medicines
- Provisional registration granted for specified time periods (2 years + up to 2 extensions, max 2 years each)
- Intended only for those medicines where further confirmatory data is still being gathered.
- Pathway subject to the provision of clear advice to consumers and healthcare professionals and any other conditions imposed by the TGA

Overview of the Provisional Approval pathway

1. Determination process

3-6 months pre-dossier

2. Pre-market registration process

As quickly as possible (max. 255 working days)

3. Provisional registration period

2 years initially (with the possibility of 2 extensions of 1-2 years each)

4. Transition to fully registered

As quickly as possible (max. 255 working days)

Considerations for Implementation in Australia

Products approved via expedited pathways

New Active Substances (NAS)

	Total NAS approvals	'Priority'	'Provisional'
EMA	28	5 (18%) *accelerated*	7 (25%) *conditional*
FDA	22	15 (68%)	6 (27%) *accelerated*
PMDA (Japan)	48	22 (46%)	-

- **1st Priority medicine registered on 30 January 2018**
  - ✓ Alectinib (Alecensa), Extension of Indication

- **2nd Priority medicine registered on 23 February 2018**
  - ✓ Emicizumab (Hemlibra), New chemical entity

Adapted from CIRS 2016 R&D Briefing # 62

Priority determinations

- 14 Priority determinations received as of 28 February 2018
- 10 (71%) Priority determinations approved
  - 6 Extension of Indications (EOI) , 4 - New Chemical Entities (NCE)
  - 70% anticancer pharmaceuticals
- Rejection reasons – Failure to meet criteria
  - #3 – comparison against existing registered therapeutic goods
    - Criteria 3 challenging: Example Interferon for Melanoma but < 100 patients per year
  - # 4 – Major therapeutic advance

Approval times: TGA Experience 2004-2018

Product Name	Pathway	Year approved	Working Days
Cervarix Human Papillomavirus Vaccine Types 16 &18	Standard with rolling submissions	2007	81
ADT Vaccine diptheria and tetanus vaccine	Standard	2006	81
Isentress (Raltegravir)	Standard – priority status	2008	82
Imbruvican (Ibrutinib) -140mg		2015	88
Panvax pandemic influenza vaccine	Standard with rolling submission	2008	91
Gardasil (HPV recombinant vaccine)		2006	92
Opdivo-nivolumab	Standard	2016	94
Alecensa (Alectinib)	**New Priority Pathway**	**2018**	**98**
Lucentis (ranibizumab)	Standard – priority status	2007	99
Alimta (pemetrexed)	Standard – priority status	2004	102
Hemlibra (emcizumab)	**New Priority Pathway**	**2018**	**104**

Safety Considerations

Research

JAMA | Original Investigation

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

- 32% novel therapeutics affected by a post market safety issue
- Accelerated and near-regulatory deadline approval statistically associated with higher events

Safety Considerations – Priority pathway

- Based on full data set
- Additional pharmacovigilance issues not expected
- Additional efficacy data not specified
- May have up to 7 EOI for one New Chemical Entity (NCE) or New Biological Entity (NBE)
- Safety signals may be from another therapeutic area
- Does Faster review increase risk to patients?

Safety Considerations – Provisional pathway

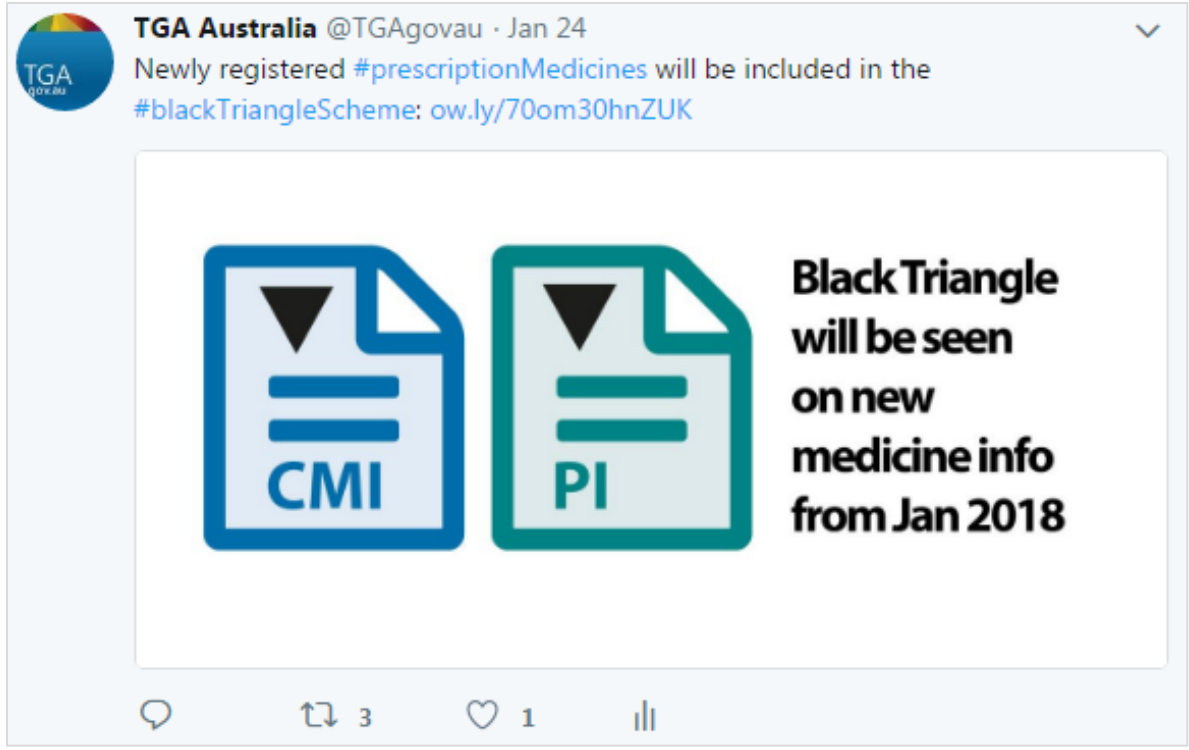
- Early data – could be NCE or NBE
  - Increased risk due to limited patient exposure
- Early data for an EOI for already registered NCE/NBE
  - Increased risk if new dose or patient group
- We will allow pre-specified updates to the dossier
  - Will this provides ability to deal with safety issues quickly?
  - Will this be enough to update PI and CMI?

Safety considerations – Provisional Pathway

- New powers under the Act for provisionally registered medicines to:
  - reduce the class of persons for whom the medicine is suitable
  - to change the directions for use
  - to add a warning or precaution
  - change the Product Information related to the medicine
- Gives delegates confidence to make a decision
- Provides TGA ability to protect patients if unexpected problems occur

Enhanced Vigilance Framework

- Provisional medicines prioritised in enhanced vigilance framework
  - Black Triangle Scheme
  - PI Reformat
  - Inspection program
  - RMP Compliance Monitoring
  - Improved Adverse Event Management System (AEMS)



Confirmatory Trials

Perspective

The Fate of FDA Postapproval Studies

Steven Woloshin, M.D., Lisa M. Schwartz, M.D., Brian White, B.A., and Thomas J. Moore, A.B.

Evaluated 614 requirements made in 2009-2010

- 20% of studies had not been started after 5-6 years
- 25% were still ongoing
- 9% delayed, 16% on schedule
- 54% completed as of 2015

Confirmatory Trials: TGA approach

- Provisional intended only for those medicines where further confirmatory data can be collected
- 2 year checkpoint to assess progress on clinical trial plan
    - Flexible approach needed as a smaller regulator
- Requirement for Sponsor to have a clinical trial plan at determination stage
- Planned trials to be fully accrued at determination stage
- Other sources of real world data?

Other Consideration: Quality & Outcomes

Format: Abstract

JAMA. 2017 Aug 15;318(7):626-636. doi: 10.1001/jama.2017.9415.

Characteristics of Preapproval and Postapproval Studies for Drugs Granted Accelerated Approval by the US Food and Drug Administration.

Naci H[1], Smalley KR[1], Kesselheim AS[2].

Author information

CONCLUSIONS AND RELEVANCE: Among 22 drugs with 24 indications granted accelerated approval by the FDA in 2009-2013, efficacy was often confirmed in postapproval trials a minimum of 3 years after approval, although confirmatory trials and preapproval trials had similar design elements, including reliance on surrogate measures as outcomes.

Other Considerations: Communicating Risk

- Standard wording in Consumer Medicine Information (CMI) & Product Information (PI)
- Consumer and Health Professional Communication Plan
- Improving Access to CMI
- Reformating of CMI
- Black Box warning
- Promotion of provisional medicines – Industry may consider Medicines Australia Code of Conduct

Other Considerations

- Pressure from sponsors and patient groups
- Media interest – short response times
- Access vis a vis protection
- Regional obligations
  - Criteria applies to Australia context only

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NOVEMBER 27 2017

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Malcolm Turnbull's Parliament gambit risks delaying access to life-saving drugs

Adam Gartrell

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A plan to give seriously ill Australians faster access to potentially life-saving drugs could be delayed because of Prime Minister Malcolm Turnbull's decision to cancel a week of lower house sittings.

The government has promised to introduce a fast track for drug approvals that would give patients access to promising new prescription medicines up to two years earlier than under the current system.

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News

TGA in line for bumper 2018 approvals

Posted 17 January 2018

The TGA approved a total of 34 new products over 2017, acco its website, making it a lower-than-average year for the regula although overseas approvals predict an influx of 2018 registr

Other options for Early access

	Medicine Applications approved/Notifications (Jul 2016- June 2017)
Special Access Scheme	68,287
Clinical trials	705 (new trials)
Authorised Prescriber	764

Reasons

- Not commercially viable in Australia
- Unproven therapy
- Novel or new therapy
- Travellers bringing products from overseas
- Compassionate Access
- Pre- provisional registration
- Lapse of provisional registration

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