



Australian Government
Department of Health
Therapeutic Goods Administration

The Australian and International landscape – keynote forum

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TGA Health Safety
Regulation

Prescription Medicines



A different medicine product mix coming through
More extensions of indications for cancer medicines

The new facilitated review pathways – how do we compare with EMA and FDA ?

Orphan drugs

Biosimilars

Clinical trials – complexity and safety

A different product mix coming through - Many more oncology drugs

- In 2017 **over 50% of global industry revenue (AUD \$700bn) total will be from oncology drugs** - eclipsing cardiovascular and metabolic drugs
- Histology-based diagnosis and chemotherapy – becoming redundant?
- Move to “**tissue agnostic**” **drug development** for cancers

Regulatory impacts

- Debate on use of surrogate endpoints / bio-markers for determining **efficacy**
- Drove much of the impetus for **priority review** and **provisional approval pathways**
- Move from organ-based to **molecular definitions** of cancer has driven companion diagnostics and **many submissions for extension of indications**
- Evaluation of results from **new and different trial designs** is challenging
- **Combinations of drugs** are being trialled

Complexity of therapies

Current (non- chemotherapy) cancer treatments

- Oncolytic virus
- Immunotherapy - T-cell stimulators
- CAR (Chimeric Antigen Receptor) - T cells
- Targeted therapies – mutation specific, individualised
- Interleukin/ interferon use

Near-Future therapies

- More bi-specific antibodies
- Macrophage stimulators
- Natural Killer cell stimulators
- Dendritic cell stimulation
- Multi-drug delivery proteins

- Viral vector treatments for haemophilia
- CAR-T + targeted therapy / immunotherapy combinations

Complexity of trial designs

Medicines	Trial designs	Trial methodologies
Targeted therapies	Pre-phase 3 for registration	Extension phase 1 trials
Immunotherapies	Trials without Overall Survival as endpoint	Population pharmacokinetics
RNA transcription blockers	Historical comparators	Adaptive trials
Engineered drug-delivery proteins	Bayesian (adaptive) designs for early phases	Drug-disease modelling e.g. in neurodegenerative diseases
Bacterial/viral therapies	Bayesian methods for registration trials	



An increasing focus on extension of indications for oncology medicines

While the quality and preclinical data remains the same, the clinical data will be new in each EoI submission.... still a lot of work for TGA's evaluators



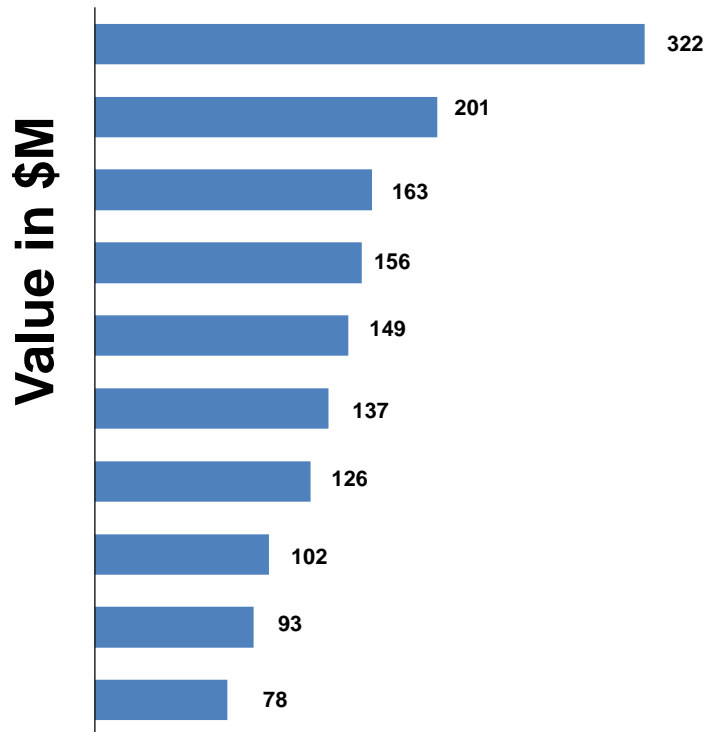
Changes to the TGA Orphan drugs program

- Retaining incentive of a **100% fee waiver**
- A **more generous orphan disease prevalence** (1 in 2000 people), or lack of financial viability for drug without fee waiver
- New pathway for orphan designation for **new dosage forms**
- **Clearer requirements**
 - proposed condition to be seriously debilitating or life threatening
 - treat conditions for which **no therapeutic goods are registered**, or that can provide **significant benefit** over current products
 - orphan **indication to be medically plausible** (distinct disease or condition), with subgroups only appropriate where product would be ineffective in the remaining population
 - the validity of the orphan designation **lapsing after six months**

Many more orphan drugs coming to the market

- **Now a mainstream business model**
 - molecular targeting, smaller clinical trials
 - 19% of all medicines sales, growing 12% pa
- **US FDA also provides** tax credits, free scientific guidance, funding for clinical studies and 7 year market exclusivity for orphan drugs
- **EMA also provides** fee relief for SMEs, free protocol assistance and 10 year market exclusivity for orphan drugs
- **With TGA's funding model** it would be difficult to provide benefits beyond fee relief

The 'wave' of patent expiries



Adalimumab (Humira)

Ranibizumab (Lucentis)

Etanercept (Enbrel)

Rituximab (Mabthera)

Trastuzumab (Herceptin)

Insulin Glargine (Lantus)

Infliximab (Remicade)

**Insulin Aspart
(Novomix, Novorapid)**

Bevacuzimab (Avastin)

Pegfilgrastim (Neulasta)

Expiry

2020

2018

Expired

Expired

Expired

Expired

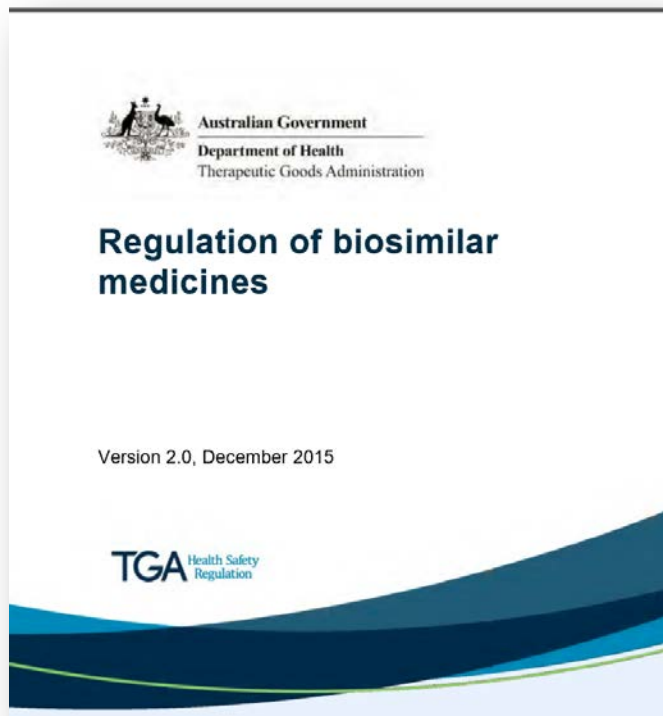
Expired

2017

2020

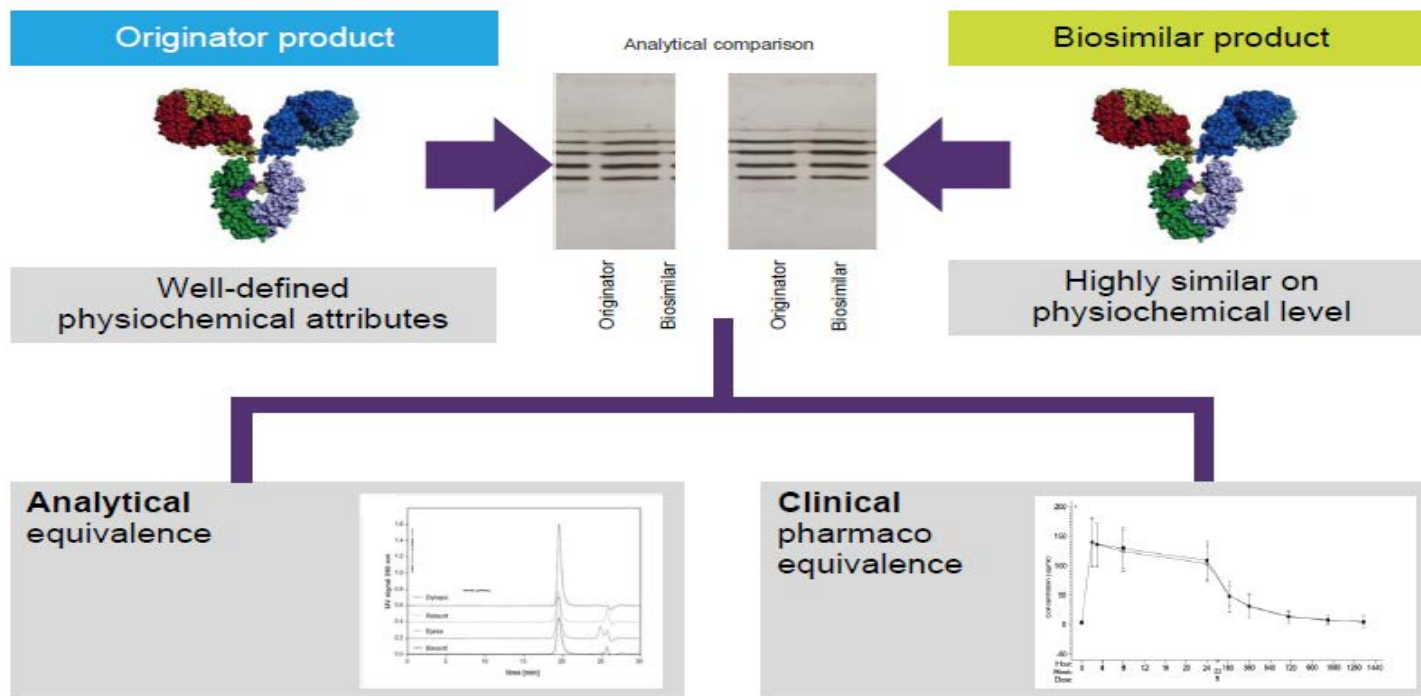
2017

Many biosimilars are on their way...



- Data Requirements/ Comparability
- Extrapolation of Indications
- Naming consultation underway
- Is a bespoke evaluation pathway needed?
- PI requirements
- First biosimilars soon to be dispensed in community pharmacies
- Post Registration – what do switching data tell us?

Regulatory evaluation of biosimilars seeks to determine analytical and clinical similarity





FDA biosimilar developments

- **Nomenclature:** FDA - designated meaningless four - letter suffix to be applied to both biosimilar and originator biologicals
- New guidance on **clinical pharmacology data required** to support demonstration of biosimilarity to a reference product
- **Guidance on interchangeable biosimilars:** data from switching studies will be required to demonstrate interchangeability
- **Slow progress** – only 5 biosimilars in US as of 30 June and no interchangeable ones yet



Biosimilars naming consultation (closes 8 Sep 17)

- **Currently**, Australia aligns with the EMA approach whereby the active ingredient in a biosimilar and its reference medicine are given the same International Non-proprietary Name
- **Is there a need in Australia for additional naming requirements** for all biological medicines (not just biosimilars) as a way of strengthening traceability and pharmacovigilance?
- **Four options** identified for feedback
 - Maintain the **status quo**
 - Maintain the **status quo with additional activities** to promote inclusion of identifying information such as a product's trade name, AUST R number and batch number in adverse event reports
 - Further align with EMA by adopting a **barcode system**
 - Adopt a **suffix-based system** in alignment with FDA's

Priority review of medicines – how does the new Australian pathway compare?

- **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances (target 150 working days)
- **Serious condition** – the medicine is indicated for the treatment, prevention or diagnosis of a life threatening or seriously debilitating disease or condition; AND
- **Unmet clinical need** – the medicine addresses an unmet clinical need in Australian patients; AND
- **Substantial** evidence **demonstrating** that the medicine provides a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered in Australia

The new Australian priority review pathway vs EMA and FDA pathways

EMA

- **PRIME (Priority Medicines) scheme**
 - address unmet clinical need and may provide major therapeutic advantage
 - scientific advice and increased EMA engagement at phase 1 stage

FDA

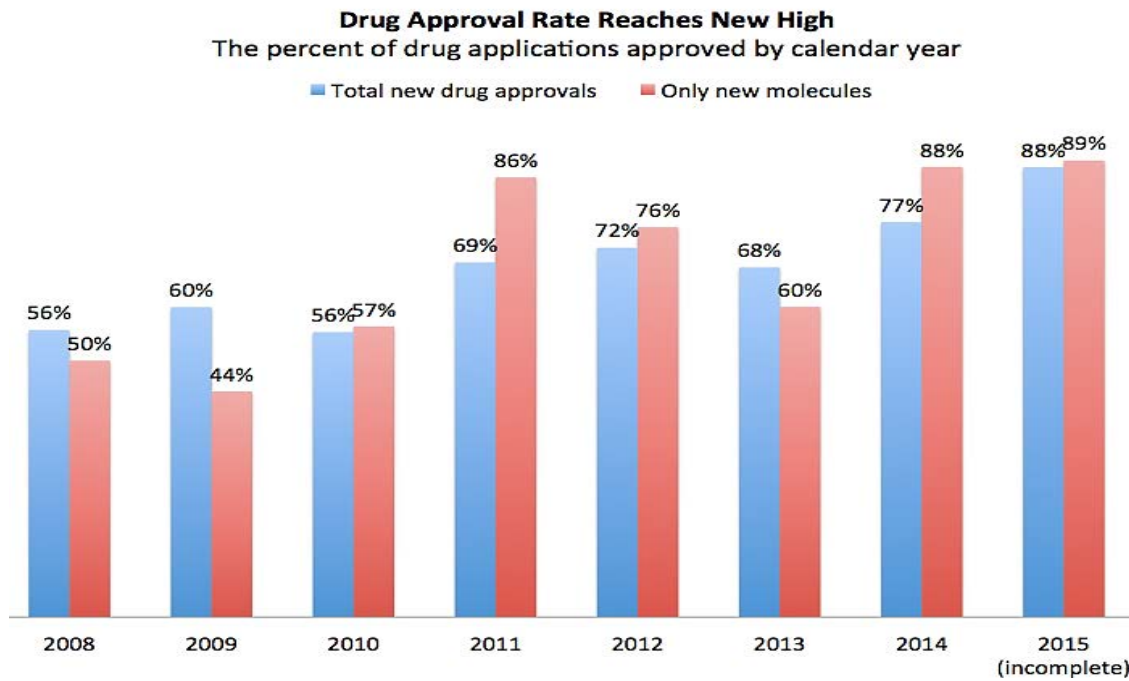
- **Priority review** - drug with potential to be a significant improvement in safety or effectiveness - review time of 6 calendar months
- **Accelerated approval** - effect on a surrogate endpoint that is reasonably likely to predict clinical advantage over existing therapies for a serious condition
- **Breakthrough designation** - preliminary clinical data demonstrates potential for significant improvement – receive extensive advice from FDA
- **Fast track** – early evidence (animal, in vitro or clinical), advice to optimize clinical trials development and rolling review of submission

Mixed support for rapid FDA approvals

- ***Faster drug approvals set the bar too low*** Davis et al, *BMJ* 354:265 (2016)
“Early approval assumes that reliable new data on benefits and harms will ensue rapidly..... but the evidence does not support these assumptions”
- ***Accelerated Approval and Expensive Drugs – a challenging combination*** Gellad and Kesselheim *NEJM* 376:2001(2017)
- ***Postapproval studies of Drugs initially approved by FDA on the basis of limited evidence*** Pease et al *BMJ* 357:1680(2017) *“Few controlled studies published after approval confirmed superior efficacy”*
- ***Are Drug Regulators really too slow?*** Marciniak and Serebruany, *BMJ* 357:67(2017)
“Delays by drug companies in submitting applications had the greatest variation.... represent the best opportunity to speed up approval”
- ***“FDA breakthrough designation can mislead patients...to give them unjustified confidence”***
Krishnamurty *JAMA Int. Med.* 175:1856(2015)
- ***“Too fast or too slow? Public disagrees over pace of FDA new drug approvals”*** –
www.researchamerica.org/release_23feb15-americanaspeaks)
- ***“FDA may be approving many costly, toxic drugs that do not improve overall survival”*** Kim and Prasad, *JAMA Int Med.* 868, 19/10/15

“The FDA Is Basically Approving Everything. Here's The Data To Prove It”

www.forbes.com/sites/matthewherper, 20/8/15



Is this a result of

- FDA providing more feedback to sponsors during development?
- Greater use of surrogate endpoints?
- Acceptance of earlier stage data e.g. for oncology trials?

Provisional licensing – proposed Australian pathway

- Provisional Approval on the basis of ***promising*** evidence from ***early data*** that the medicine is likely to provide a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered
- Following **evaluation of a more limited data dossier** than would be required for standard registration process
- New system to be **implemented by mid-2018** (requires TG Act change)
- **Likely to involve:**
 - Provisional registration **for a specified time** (2 years?)
 - **Sponsors will be required** to submit post-market safety and efficacy data
 - **Enhanced post-market monitoring** by both the medicine sponsor and TGA
 - Medicines **re-evaluated for full registration** when enough data is provided to confirm adequate safety and efficacy standards
 - **Provision of advice to consumers and health** practitioners about the provisional nature of the approval

Provisional licensing in other countries

- **EMA conditional licensing (one year renewable)**
 - Often for medicines with incomplete data e.g. on stability rather than for the most innovative products
- **US accelerated approval (not “provisional” as not time-limited)**
 - Use of a surrogate endpoint as basis of trial design and approval, confirmatory trials should be underway at time of approval
- **Sweden** adaptive approval – only for certain conditions e.g. Alzheimers
- **Japan** – Sakigake schemes for Japanese-developed products
 - Medicine priority reviews, extension of indications with less evidence
 - provisionally licensing of cell and tissue therapies

Implications for reimbursement being addressed in all countries

Clinical trials – a key source of uncertainty

- **Australian trial sponsor** carries medico-legal responsibility
- **TGA's focus** is on access to unapproved products for trials rather than end-to-end regulation of trials – mature HREC system in Australia
- **Majority of trials are notified to TGA** (CTN) with formal approval (CTX) only mandated for class 4 biologicals
- CTN model stimulates local trials, but **some questions over**
 - **Combination products** – with different sponsors – can make rapid action challenging when there are safety issues
 - **Small numbers of participants** at each site – often overseas company/ investigator has the critical information
 - Oversight of “**first in man**” / **Phase 1 studies**
 - **Oversight more broadly with new trial designs**
 - Several states and NHMRC currently reviewing trial oversight

New clinical trial notifications to TGA for medicines by phase (NCEs/ new indications)

	2015-16
Phase 1	205
Phase 2	217
Phase 3	301
Phase 4	146
Bioavailability/equivalence	39
None specified	134

We have focused a lot on benefit and risk, but not enough on uncertainty





Can regulators manage uncertainty well enough?

- **Regulators** have frameworks for assessing benefits and harms (risk) but less with uncertainty
- **Uncertainty and harms** can be confused, with negative consequences for decision making
- There will be more uncertainty with **medicine submissions that have less clinical data** – e.g. orphan drugs, provisional approval
- Some of the **newer clinical trial designs** provide less certain results

What happens if the wrong decision is made on market authorisation?

The good, the bad and the useless

Allowed on market?	Drug is harmful ('bad' drug)	Drug is safe and beneficial ('good' drug)	Drug may be safe, but is useless ('futile' drug)
Yes	Patients at risk (toxicity)	Appropriate decision	False hope, wasted money
No	Appropriate decision	Patients lose out	Appropriate decision

Sipp D et al. Nature 543 (2017) 174 doi:10.1038/543174a

Medical Devices



Regulation of new device technologies

Implementation of TGA clinical evidence guidelines for devices

Companion diagnostics – how to align medicine and IVD reviews ?

Software as a medical device

Harmonisation of device reforms with the European Union

- **New EU regulations** came into effect 25 May 2017
 - Greater NB oversight and concerns re delays
 - stricter clinical evidence requirements with no grandfathering, device reclassifications
- **MMDR recommended that** Australian regulation of devices is, wherever possible, aligned with the EU framework
- We have commenced **detailed comparison** of Australian and new EU requirements
- Initial consultation currently open, rest planned for the first half of 2018

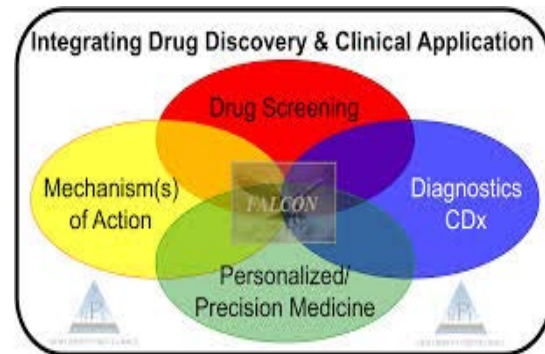


The first tranche – patient safety

- Consultation open on **two measures** to further align Australian and European medical device regulatory requirements:
 - Reclassification of all implantable **surgical mesh devices** from Class IIb (medium to high risk) to Class III (high risk)
 - Introduction of requirements for medical device manufacturers to provide patient implant cards and product information **for all active and implantable medical devices**
- The TGA is looking for views from industry, healthcare professionals, and current (and future) recipients of devices - to identify issues and address any unintended consequences
- Consultation closes 25 August

Many more oncology drugs means more companion diagnostics

- **Greater use of bio-markers** for determining target populations
- Drove much of the impetus for **priority review** and **provisional approval pathways for medicines**
- Move from organ-based to **molecular definitions** of cancer has driven companion diagnostics and **many submissions for extension of indications**
- **TGA required to align parallel pathways of product evaluation** – logistically complex if different sponsors and issues arise with one product



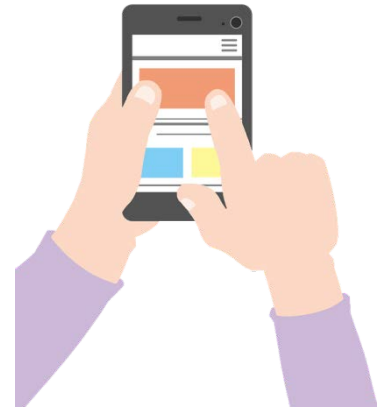


Regulation of 3D printed devices

- “Patient – specific technology”, 3D bio-printing and personalised implants may fit the definition of a custom-made device under the Therapeutic Goods Act
 - **Custom-made devices** are exempt from inclusion on the ARTG,
 - Australian manufacturer or importer **must notify** its details to TGA
 - And they are still **required to report adverse events**
- How does **regulation keep up with technological change?**
 - What evidence should a **clinical trial** for 3D printed device collect?
 - How to **manage innovations** such as customised joint implants?
 - e.g. FDA now requires “**patient-matched**” **3D printed devices** to undergo pre-market assessment
- **TGA/ industry /researcher workshop** held on Aug 10

Developments create regulatory dilemmas

- **Medical Apps:** software is considered a medical device if used for diagnosis, prevention, monitoring, treatment or alleviation of disease...
 - **Apps that analyse clinical data**, e.g. results of blood tests or ECGs
 - **Embedded software** in monitors, defibrillators, pumps and implantable devices
- Software that just **presents or manages information** e.g. medical records, dosage calculator is not a device





Cross cutting issues

Transparency

- Major **changes in community expectations of government** over the last 20 years e.g.
 - Publish business plans, annual reports
 - Freedom of Information laws
 - Statements of reasons for decisions
 - Testify before Parliament
- Have **regulators been slow to act** here?
 - Industry commercial confidentiality issues may be a factor

Now an increased emphasis on regulatory transparency, including publication of:

In Australia

- **Information on adverse events, product cancellations, and reasons for cancellation**
- **Enforcement information** such as advertising complaints
- Information on **recently approved medicines**
- **Successful designations** for accelerated, provisional and orphan drugs – coming soon!
- **Information on positive and negative decisions** for medicines
- Reporting against KPIs and **information on business performance** (approval timeframes, numbers of products approved, compliance information)

In other countries e.g.

- **GMP Inspection** information findings/reports (Canada, US)
- **Information on new prescription medicines** that are currently under review (Canada, EU)
- Access to (patient de-identified) **clinical trials** data (EU)
- **Pre-market advisory committee meetings** held in public (US)
- **Open hearings on safety reviews** for particular medicines (EU)
- More information on **approved medical devices and decision documents** (US, Canada, Japan)
- **Mandatory reporting of device adverse events** by healthcare facilities (Brazil, Canada, Denmark)

Europe and Brexit

- Vote on **relocation of EMA HQ** due in November
- **Uncertainty about relationship** of UK MHRA with EMA or with European Device system post Brexit
- MHRA UK looking for **closer relationships with TGA** and several other regulators
- **Concerns about workloads** at MHRA and delays in UK drug launches
- **EMA advising companies** to transfer market authorisation of products from UK to Eur Economic Area (EU, Norway, Iceland and Liechtenstein)
- Qualified person for **pharmacovigilance** must also reside in EEA (but most currently are in the UK)
- **Concerns with regulatory review workloads** in absence of the UK MHRA



Some US developments

- Reignited “**right to try**” debate
- Publication of **patient experience data** with new drug applications
- **Prescription opioid misuse** is top priority of new FDA Commissioner
- White House calls for **full cost recovery**, but FDA remains 40-50% taxpayer funded
- **Cybersecurity focus** – e.g. medical device hacking; GMP data integrity
- **Stronger FDA-EMA alignment**, particularly on GMP and pharmacovigilance
- Lack of clarity about **future regulation of lab-developed IVDs**
- **Some class II devices** removed from 510/k requirement

So what will define a comparable overseas regulator?





Conclusion: keeping up with developments – technological, international, societal in modernising regulatory frameworks is critical

TGA evaluators
keeping
up with the science

AND

having appropriate regulatory
frameworks
are both important

As we go through significant
regulatory reforms

.....

We are learning from international
experience

.....

but adapting this to the Australian
situation



Australian Government

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