What’s trending in medicines regulation?
A January 2017 reflection

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ARCS Seminar, Sydney

24 January 2017
What’s trending in medicines regulation?
A January 2017 reflection

• **How do we compare?** Medicine approvals and timeframes

• Some **international medicines industry and regulatory trends** and their relevance for TGA

• **A different product mix coming through** - more orphans, extensions of indications for cancer medicines and biosimilars

• **Uncertainty will become more significant for regulators and industry**, and is just as important and benefit/risk (harms)

• **Clinical trials** - complexity and safety

• **Real world and big data** - becoming more central to registration and pharmacovigilance

• **Innovation in technology** and how regulators must respond

• **Conclusion**
# How do we compare? Approval times

<table>
<thead>
<tr>
<th></th>
<th>NCE Median approval time</th>
<th>NCE Median approval time</th>
<th>Number of medicines market authorisation staff</th>
<th>Variation in NCE approval times (approx. days)</th>
<th>NCEs put through expedited pathways</th>
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<tbody>
<tr>
<td></td>
<td>calendar days</td>
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<td>313</td>
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* takes into account that evaluations are carried out by member agencies
2015 Data from CIRS R&D briefing 59
How do we compare? Approval numbers

• In 2016 - 39 New Chemical Entity (NCE) Registrations by TGA vs 22 by FDA
  – Many more than FDA !!!

• The 2015 situation was the other way around
  – 27 New Chemical Entity (NCE) Registrations by TGA vs 45 by FDA

• Also for TGA in 2016:
  – 37 Extension of Indications (EOI) Registrations
  – 18 Orphan Drug Designations made
Some innovative/first in class cancer drugs approved in 2016

- **Empliciti (elotuzumab)** - multiple myeloma - targets the cell surface SLAMF7 (Signalling Lymphocytic Activation Molecule Family member 7) glycoprotein, and activates the immune system to attack and kill cancer cells.

- **Farydak (panobinostat)** - multiple myeloma - inhibits histone deacetylases and slows the growth of plasma cells.

- **Lenvima (lenvatinib)** - differentiated thyroid cancer - blocks the activation of VEGF which reduces the growth of cancer cells.

- **Lynparza (olaparib)** - epithelial ovarian, fallopian tube, or primary peritoneal cancer with BRCA - inhibits defective DNA repair process.

- **Opdivo (nivolumab)** - melanoma, non-small cell lung cancer, or advanced clear cell renal cell carcinoma - immune checkpoint inhibitor.

Other innovative/first in class drugs approved in 2016

- **Briviact (brivaracetam)** – epileptic seizures - binds to the synaptic vesicle protein 2A and inhibits presynaptic calcium channels

- **Praluent (alirocumab)** - patients who are unable to control their low-density lipoprotein (LDL) cholesterol in addition to diet, exercise and other cholesterol-lowering drugs. Targets pro-protein convertase subtilisin kexin 9 (PCSK9) that otherwise reduces the number of receptors on the liver that remove LDL cholesterol from the blood.

- **Zinbryta (daclizumab)** - multiple sclerosis (MS) - targets the CD25 subunit of interleukin 2 (IL-2) receptors on reactive T cells, reducing and preventing inflammation
Innovative combination therapies approved in 2016

- **Entresto** - chronic heart failure - sacubitril (controls blood volume and lowers blood pressure) and valsartan (keeps blood vessels from narrowing to improve blood flow)
- **Genvoya** - complete regimen for the treatment of HIV-1 infection - elvitegravir (blocks an HIV integrase), obicistat (increases the effectiveness of elvitegravir), emtricitabine and tenofovir alafenamide (block reverse transcriptase)
- **Odefsey** - complete regimen for the treatment of HIV-1 infection - emtricitabine, rilpivirine, and tenofovir alafenamide
- **Orkambi** - for cystic fibrosis in people with two copies of the F508del mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Lumacaftor increases the number of CFTR proteins trafficked to the cell surface, while Ivacaftor increases the probability the defective channel will open and allow chloride ions to pass through.
- **Zepatier** - for genotype 1 and 4 chronic hepatitis C virus - elbasvir (prevents transcription of the HCV RNA) and grazoprevir (prevents cleavage of the necessary polyproteins for replication)
Many more oncology drugs

- In 2017 over 50% of global industry revenue (AUD $700 bn) total will be from oncology drugs - eclipsing cardiovascular and metabolic drugs
- Histology-based diagnosis and chemotherapy - becoming redundant?
- 18 novel therapeutic mechanisms described at ESMO and ASH in 2016
- Some commentators have questioned cost versus progression free survival

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

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Trial designs</th>
<th>Trial methodologies</th>
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<tbody>
<tr>
<td>Targeted therapies</td>
<td>Pre-phase 3 for registration</td>
<td>Extension phase 1 trials</td>
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<tr>
<td>Immunotherapies</td>
<td>Trials without Overall Survival as endpoint</td>
<td>Population pharmacokinetics</td>
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<tr>
<td>RNA transcription blockers</td>
<td>Historical comparators</td>
<td>Adaptive trials</td>
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<td>Engineered drug-delivery proteins</td>
<td>Bayesian (adaptive) designs for early phases</td>
<td>Drug-disease modelling e.g. in neurodegenerative diseases</td>
</tr>
<tr>
<td>Bacterial/viral therapies</td>
<td>Bayesian methods for registration trials</td>
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What's trending in medicine's regulation?
The clinical data will be new in each Eol submission .... so it’s still a lot of work for TGA’s evaluators
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

• **TGA reviewing its policies, e.g.**
  – Population/prevalence threshold
  – Definition of serious condition
  – No satisfactory alternative or new treatment is significant benefit over these

• **EMA also updating policies e.g.**
  – meaning of "significant benefit"
  – application to emerging diseases
  – where two products assessed simultaneously
  – extension of indications
Many biosimilars are on their way…

- Data Requirements/Comparability
- Extrapolation of Indications
- Naming – still to be finalised
- 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?
Some (very) recent FDA developments

- **US Supreme Court** to review whether biosimilar sponsors have to wait 6 months after FDA products before being permitted to launch their products.

- **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.
## The ‘wave’ of patent expiries

<table>
<thead>
<tr>
<th>Value in $M</th>
<th>Expiry</th>
<th>Product</th>
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<tbody>
<tr>
<td>322</td>
<td>2020</td>
<td>Adalimumab (Humira)</td>
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<tr>
<td>201</td>
<td>2018</td>
<td>Ranibizumab (Lucentis)</td>
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<tr>
<td>163</td>
<td>Expired</td>
<td>Etanercept (Enbrel)</td>
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<tr>
<td>156</td>
<td>Expired</td>
<td>Rituximab (Mabthera)</td>
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<tr>
<td>149</td>
<td>Expired</td>
<td>Trastuzumab (Herceptin)</td>
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<tr>
<td>137</td>
<td>Expired</td>
<td>Insulin Glargine (Lantus)</td>
</tr>
<tr>
<td>126</td>
<td>Expired</td>
<td>Infliximab (Remicade)</td>
</tr>
<tr>
<td>102</td>
<td>2017</td>
<td>Insulin Aspart (Novomix, Novorapid)</td>
</tr>
<tr>
<td>93</td>
<td>2020</td>
<td>Bevacuzimab (Avastin)</td>
</tr>
<tr>
<td>78</td>
<td>2017</td>
<td>Pegfilgrastim (Neulasta)</td>
</tr>
</tbody>
</table>
Priority review and provisional licensing

Priority review

• Several US pathways – Breakthrough designation, priority review
• EMA PRIME (PRIority MEdicines) system – proactive early dialogue
• Japanese regulatory framework for innovative products (SAKIGAKE)
• Australia will introduce in 2017

Provisional/adaptive licensing pathways

• EMA conditional licensing
• Sweden adaptive approval
• Japan - provisionally licensing cell and tissue therapies
• Australia will introduce in 2018

Implications for reimbursement being addressed in all countries
New pathways are coming at TGA

Source: Freelimages.com/leagun
Expedited pathways for prescription medicines

- **Priority Review** of a complete data dossier within a reduced timeframe in certain circumstances (target 150 working days)

- **Provisional Approval** on the basis of early data on safety and efficacy, where the immediate availability of the medicine outweighs the uncertainty around additional data still being required

- Both **facilitate earlier access to medicines** that address unmet clinical need without compromising safety, efficacy and quality

Source: FreelImages.com/Jean Scheijen
Proposed eligibility criteria to be finalised following consultation

- **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

- **Major Therapeutic Advantage**
  
  For Priority Review: *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

  For Provisional Approval: *promising* evidence from *early data* indicating that the medicine is likely to provide a major therapeutic advantage in efficacy and/or safety over existing treatments that are fully registered.
Provisional Approval

• Following **evaluation of a more limited data dossier** than would be required for standard registration process

• **Public consultation** will be undertaken in Feb-Mar 2017

• New system to be **implemented by mid-2018** (requires Act change)

• Likely to involve:
  – Provisional registration **granted for a specified time** (2-3 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 to be **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
“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don’t know. But there are also unknown unknowns. There are things we don’t know we don’t know.”

(Donald Rumsfeld)
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.
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)

<table>
<thead>
<tr>
<th>Phase</th>
<th>2015-16</th>
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</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>205</td>
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<td>Phase 2</td>
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<td>Phase 3</td>
<td>301</td>
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<tr>
<td>Phase 4</td>
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<tr>
<td>Bioavailability/equivalence</td>
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<tr>
<td>None specified</td>
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</table>
Increased focus on real world data

**Market authorisation**
- Efficacy, comparators and effectiveness data
- Use of patient centred outcome data
- **Integration of drug and biomarker development** for cancers
- **Focus on challenging conditions** for drug development – e.g. Alzheimer's, diabetes
- **Parallel scientific advice** with European HTA Bodies, FDA-Medicare/ Medicaid

**Innovative approaches to pharmacovigilance**
- Stimulated reporting for new medicines
- Use of “big” data, such as electronic health data, registries
- Use of social media posts for pharmacovigilance?
Data linkage analysis

Linkage of patient de-identified pharmaceutical and medical benefits data

- Preliminary data linkage projects have shown that PBS and MBS data can be used to look at potential safety signals
- Methodological challenges exist as MBS may not capture all health services provided, or in sufficient granularity.
Challenges in the collection and use of real world data

• For many drugs, **systematic collection of data may stop** once they receive market authorization or reimbursement
  – If data is collected it may focus on adverse reactions not effectiveness

• **Real World Data is dispersed** in hospitals, private practices, with insurers and patients – and incentives to collect data may be limited

• **Validity of RWD** may be hard to confirm and sources poorly connected

• **Registries, electronic health records and big data** may address some of these issues, but
  – Use of different data standards makes it hard to combine data sets
  – Data linkage for data collected for different purposes difficult to achieve
  – Regulatory and privacy constraints to transferring data
  – Are health records detailed enough to determine specified outcomes?
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

Source: FreeImages.com/Josh Klute
Now an increased emphasis on regulatory transparency, including publication of:

- Information on product cancellations, and reasons for cancellation
- GMP Inspection information and reports
- Enforcement information such as advertising complaints
- Information on recently approved medicines
- Information on new prescription medicines that are currently under review
- Information on positive and negative decisions for medicines
- Access to (patient de-identified) clinical trials data
- Reporting against KPIs and information on business performance (approval timeframes, numbers of products approved, compliance information)
Conclusion: keeping up with developments – technological, international, societal and modernising regulatory frameworks is critical

Keeping TGA’s evaluators up with the science AND having appropriate regulatory frameworks are both important

Source: Freimages.com/renata jun