Impact of innovative therapies on the regulation of therapeutic goods

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ARCS Melbourne 26 Nov 2015
The nature of medicines has changed... and their regulation has had to evolve too

- Move from small molecules to protein drugs and biologicals
- Targeting of niche therapies rather than “blockbuster” products
- More medicine-device and medicine-IVD combinations
- Personalised medicine
Cancer therapy - from cytotoxics to MAbs to immunotherapy

• **Cytotoxics**
  – toxic to rapidly growing cell types – hard to get dose correct
  – e.g. doxacetal, cyclophosphamide, cisplatin

• **Monoclonal antibodies**
  – e.g. those targeted to cancer cell antigens e.g. trastuzumab (anti-HER2), or destroy overactive B-cells rituximab (anti-CD20)
  – also antibody-drug conjugates, bispecific antibodies

• **Blocking negative immune regulators ("checkpoints")**
  – can give the immune system ability to fight cancers
  – e.g. T-cell activation by blockade of CTLA-4 by ipilimumab or PD-1 by pembrolizumab and nivolumab
After some time lag, MAb technologies are now mainstream

- Cancer and immune disorders dominate – but there are also:
  - cholesterol-lowering treatments
  - antidotes e.g. for new anticoagulants
  - antibacterial antibodies now in clinical trials
- And more MAb biosimilars are coming to the market as patents on originators expire
Changes in the commercial environment

- **Increasing drug development costs**, less local manufacture
- **Orphan drugs** have become a mainstream business
- **Shift from short-term use of therapies** (e.g. for infections) to management of chronic disease
- **Reimbursement rather than registration** often seen as the “real point of market access”
- More **near-simultaneous submissions** through e-CTD
- **Reimbursement** rather than regulatory approval more often determining “market entry”
- Need **greater simultaneous regulatory and HTA dialogue**
US expedited regulatory pathways

Qualifying Criteria: A drug that treats a serious condition AND …

1. Fast track (1997) - Demonstrates the potential to address an unmet need
   – Expedited development based on early clinical or nonclinical evidence

2. Breakthrough (2012) - Preliminary clinical data demonstrates potential for significant improvement
   – Fast track features and extensive meetings/advice from senior FDA staff

   – Review time at least four months faster
   – Most relevant pathway to MMDR recommendations

4. Accelerated Approval (1992) - Meaningful advantage over other therapies
   – Approval based on effect on surrogate endpoint or intermediate clinical endpoint that is likely to predict the clinical benefit
These have been the subject of much recent commentary

- “FDA’s breakthrough designation has got **new drugs to market** 3.5 years earlier than otherwise” – Milne, [http://csdd.tufts.edu/reports](http://csdd.tufts.edu/reports), 26/2/15

- “FDA **breakthrough designation can mislead patients** …to give them unjustified confidence in the therapy” – Krishnamurty, JAMA Int. Med. 175:1856 (2015)
  - Role of oncologists in helping patients make informed decisions

- “FDA is **too conservative** in regulating approvals for severe diseases like pancreatic cancer but not conservative for less dire cancers such as prostate cancer” – Lo and Montazerhodjat, [http://ssrn.com/abstract=2641547](http://ssrn.com/abstract=2641547), 19/8/15

- Widespread **use of surrogate endpoints** for cancer drugs questioned “FDA may be approving many costly, toxic drugs that do not improve overall survival” - Kim and Prasad, JAMA Int Med. 2015.5868, 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?
Adaptive or “provisional” licensing

- Licensing of medicines prior to full phase 3 trials subject to obtaining ‘real-world’ effectiveness and safety data through an iterative process

- Where there are prospects that regulatory requirements for expansion from a restricted indication to broader populations can be fulfilled

- A development plan is agreed to provides information on risk versus benefit to enable subsequent authorization in a defined group of patients and/or treatments

- May be best suited when
  - early data suggests a positive risk-benefit profile and there is an unmet clinical need, OR
  - regulatory data exists on safety, and proposal is for extension of indications

- Early involvement of funders and clinical groups is key
Approval would no longer be “all or nothing”?
Adaptive / provisional licensing – concerns

• Will it lead to **lowered evidence standards** from smaller studies?
• How to **avoid subjective assessment** of the benefit/risk ratio as assessment is not blind?
• What if the **committed follow-up studies** are never completed by the drug company?
• **Who will be accountable** if there is a failure associated with a product?
• Will there be **difficulties in withdrawing medicine** if efficacy is limited once a patient/prescriber cohort is established?
Clinical trial design and analysis challenges

- Experience with **surrogate endpoints** vs clinical outcomes or mortality
- How to better use **patient-defined endpoints** e.g. quality of life
- Ensure populations in trials are representative
- **Disease prevention therapies** require long-term trials, large numbers
- Benefit/risk tolerance differs for different populations and individuals
- **Personalised medicine** – adequate powering for small groups?
- **Adaptive trial designs** – data gathered during trial can enable treatments to be changed (e.g. dose escalation) midway
- Can regulators provide greater clarity on trial **design requirements**?
Comparative effectiveness trials for medicines

- TGA does approve medicines based on comparative trials
- More closely reflect decisions made in clinical practice
- **Direct comparisons** more robust than meta-analyses
- But there are challenges:
  - Often **limited differences in effectiveness** between medicines in a class
  - How would individual differences in response be addressed?
  - How to compare medicines with greater efficacy but greater harms?
  - **Choice of comparator medicine/dose** can introduce biases
Some emerging changes to clinical trials for cancer medicines

- Examination of the “exceptional responders” in clinical trials to determine if they have new markers
- Trials being organised according to genomics of the tumour rather than the organ hosting the tumour e.g. 4 genetic types of bowel cancer known
- Potential for “basket trials” of drugs for cancers with genetic similarities
- Pattern for rolling out / extension of indications of newer cancer drugs e.g. PD-1 inhibitors
Personalised medicine

• **Today:** Diagnosis and medication/treatment still predominantly based on *symptoms and their subjective interpretation* by the GP

• **Soon:** Diagnosis and treatment based on biology/genetic testing and selection of medication based on *objective evaluation of benefit/risk for the individual patient*
Current use of genetic tests

- **To predict disease susceptibility** – association analysis
- **To enable more targeted screening**
  - Inherited susceptibility to breast and ovarian cancer (BRCA 1, BRCA 2)
  - Hereditary non-polyposis colon cancer (MLH 1, MSH 2, MSH 6, PMS 2)
- **Targeted therapy** – identification of patients likely to benefit
  - Breast cancer susceptible to trastuzumab or lapatinib (HER2 over-expression)
  - Metastatic colon cancer susceptible to cetuximab (wild type KRAS gene)
  - Metastatic melanoma susceptible to vemurafenib (BRAF*V600E allele)
- **Predict adverse reactions** to particular medicines
  - Risk of fatal hypersensitivity to abacavir in HIV patients with HLA-B*5701 allele
Genetic testing is getting cheaper and simpler but interpretation is harder.

1980-2010: identify mutations in single genes that may be associated with disease
- Mendelian “Yes / no” linkage to disease / susceptibility
- But only a few diseases e.g. Huntington’s disease, cystic fibrosis, Alzheimers, some cancers are this simple genetically
- BRCA1 and 2 genes – breast, pancreatic and prostate cancer screening

Now: identify changes in the sequences of multiple genes that may be associated with disease
- Only provides “probability of association”
- Makes interpretation, counselling, decision making much harder
Individuals can reach different conclusions

Announcement in May 2013 that Angelina Jolie, carrier of BRCA1 had a preventative double mastectomy

Australian procedures then increased:
- From 597 in 12/13
- To 1256 in 13/14

Author: Foreign and Commonwealth Office
It’s not all about high tech – do you regulate faecal transplants? If so, how?

Reported efficacy in C. difficile infection, Crohn’s disease through fecal microbiome action, but risks of viral and bacterial infection in recipient.
How can regulators respond?
1. Through their regulation

- Sometimes **new regulatory frameworks** would be required
  - e.g. this was the case for cell and tissue therapies and IVDs
  - e.g. if the Government decided to bring in provisional/ adaptive licensing of medicines, and/or accelerated approval of innovative devices

- Sometimes **existing frameworks need to be modified**
  - e.g. biosimilars have to date been evaluated under the NCE pathway but an abbreviated

- But **often existing frameworks are flexible enough**, as many parts of the TG Act and Regulations are not overly prescriptive
  - e.g. fast-track pathways for medicines could be legally accommodated now
  - e.g. device apps and 3-D printed products can be evaluated now
Medical Apps - regulatory dilemmas

• Software is a medical device if *used for diagnosis, prevention, monitoring, treatment or alleviation of disease*
  - e.g. apps that analyse clinical data such as results of blood tests or ECGs
• **TGA also regulates** software used in manufacturing, for maintaining QMS, firmware/embedded software in devices
• **Software that just presents or manages information**
  e.g. medical records, dosage calculator is not a device
3D-printed devices - regulatory dilemmas

• Enables highly-customised devices fitting to individual patient body shape
• But what is their regulatory status if products are not “mass-manufactured”?
• “Custom made device” regulations designed for products like dentures and eyeglasses
• Must meet conformity assessment procedures regulated by the TGA but not required to undergo assessment by the TGA or to be included on the ARTG before supply
• Often the materials used in devices will be the regulated product (e.g. recent FDA approval of a resin used in 3D printing of dentures)
2. Through a more proactive approach

- Ensure frameworks are in place to assess new technologies
- Flexibility in product evaluation e.g. clinical trial designs
- Maintain/reruit technical skills required for emerging products - current cancer biology, cell science, software
- Support SMEs through the regulatory maze
- Stronger international regulatory collaboration
- Closer relationships with industry to understand issues
- Involvement in international forums to discuss emerging trends and align approaches to the extent possible
- Engage in developments in regulatory science
3. Through process improvement
e.g. TGA Business Improvement Program

- Continue to enable electronic submissions
- Strengthened guidelines and supporting information for sponsors and manufacturers
- Centralised data repository – single source of data a client relationship management system
- New client self-service portal for sponsors and manufacturers to:
  - check application status
  - receive invoices
  - respond to requests for information
Australian biologicals regulatory scheme introduced May 2011 (fully in place by 2014) to:

- Sets standards relating to **manufacturing processes** and standards for **individual products**
- Minimise risk of **infectious disease transmission** (TGO 88)
- Match level of regulation/classification to the level of risk/ **manipulation** of products
- Provide ability to **respond to changes in technology**
- Support greater **international alignment**
- Develop appropriate **GMP**
But biologicals bring additional regulatory challenges

• **How to classify them by risk?** By level of processing / changes in properties or likelihood of carrying transmissible disease?

• **How to develop appropriate GMP codes** recognising lack of control over starting materials and many are not batch produced?

• Can **risk of infectious disease transmission** be eliminated?
  – donor questionnaires, subjective nature of exclusion decisions
  – evolving knowledge e.g. of prion-related and degenerative diseases

• Other **unforeseen reactions** can occur, e.g.
  – with adult stem cells such as heart attack and severe thrombosis
  – demyelinating encephalomyelitis in MS treatment

• **Many biologicals cannot be recalled** once in a recipient’s body
Old stereotypes die hard - views of a regulator

The Dictionary definition doesn’t help, either

reg·u·la·tor  (rgy-ltr) n

One, such as the member of a governmental regulatory agency, that ensures compliance with laws, regulations, and established rules
Is regulatory policy evolving fast enough?

- Apart from a focus on benefit-risk assessment, **new products require more focus on managing “unknowns”** around products

- Move from “wait for an application” to “engage early with companies with new technology”

- **Off label use of therapeutic goods** - require incentives to encourage extension of indications

- **Accelerated approvals and adaptive licensing** to facilitate access

- **SMEs** often now bringing novel medicines and biologicals to market rather than big pharma companies – education needed

- How to address **change in benefit-risk balance** over time?
To conclude:

Regulatory science will be critical

- To evaluate **emerging and combination technologies**
- To understand the translation of biomarkers for regulatory use
- **Scientific approaches for embedding benefit-risk methodology**
- **Alternative clinical trial designs and analysis methods**
- Develop **toxicology science for new therapeutic products**
- Utilisation of larger data sets based on real world use for **pharmacovigilance**
- Integration of **“quality by design” approaches to GMP**
- **Social science and market research** to support consumers and health care professionals to make informed decisions
Interested in being part of this innovative journey?

- TGA currently has some contract roles available in Canberra, Sydney and Melbourne across our different areas of regulation.
- Experience working in a regulator can be very useful for subsequent industry, policy or research careers.
- Contact me through email and I can pass your expression of interest on to the right people.