International regulatory cooperation: more important than ever

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Why strengthen regional international regulatory convergence?

- Medicine and device industries and supply chains are global
- Avoid duplication of others’ efforts
- Share best regulatory practices and policy thinking
- Development of new regulatory science
- Exchange of public and confidential safety data
- Access to pharmacovigilance data from larger populations or different racial mixes
- Capacity building for emerging regulators with public health, local industry and trade benefits
Convergence not Harmonisation

not trying to establish a single regulatory system across different developed countries

• Instead it means that regulatory requirements are consistent

Challenges

• Changing established laws and regulations and regulatory philosophies may be difficult
• Avoiding ‘lowest common denominator’ outcomes
• Minimising transaction costs/ endless meetings
• Ability to make sovereign decisions remains paramount
What do we mean by worksharing?

*Use of a completed report from another regulator (information sharing)*

OR

*Where two agencies share the workload by using each other’s assessment reports (worksharing)*

- Requires “near identical” submissions, i.e. same
  - product (active, formulation, manufacturer, dose form, strength) and
  - clinical context (indications, target patient population, dose and administration, RMP?) and identical clinical datasets
- Many regulators’ legislation is not prescriptive about how the evaluation and decision making has to proceed
- Timely sharing of reports to enable their prompt review is critical
Current collaborative initiatives

- **ICH** (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals)
- **PIC/S** (Pharmaceutical Inspection Cooperation Scheme)
- **International Medical Devices Regulators Forum**
- **International Generic Drug Regulators Pilot**
- **ACSS** (Australia, Singapore, Switzerland, Canada) and **Australia-Canada Regulatory Cooperation initiatives**
  - Manufacturing compliance and enforcement
  - Generic medicines
  - Good review practices
  - Risk benefit assessment/communication methodology
  - Secure portal for information exchange
  - OTC medicines (Australia-Canada)
International GMP inspection collaboration

- Involvement in PIC/S
- Widespread use of GMP clearances already very significantly reduces the number of overseas inspections required
- Joint inspections with other regulators
International Coalition of Medicines Regulatory Agencies - formed Dec 2013

• First regulatory coalition at agency head level
  – 23 countries plus EMA, EU and WHO
  – TGA Australia is on the interim Executive Committee
• Leverage/strategic oversight of existing initiatives
• Initial priorities:
  – Better information sharing mechanisms between regulators (e.g. IT systems, commercial in confidence)
  – United industry engagement
  – GMP Inspection worksharing
  – Generic medicines convergence and worksharing
  – Capacity building of emerging regulators

International regulatory cooperation: more important than ever
A worked example - generic medicines

- Pressures facing regulators of generic drugs from the increasing numbers of marketing applications and complexity of products.
- At the same time, access to affordable, quality generic drugs increasingly important in containing health care costs.
- Need to increase efficiency of review process - information exchange – coordination – responsiveness.

International regulatory cooperation: more important than ever
Vision for generic medicines

• To establish a global system to assist the assessment of generic medicines

• Coordination of applications would be facilitated, with assessments performed by participating regulatory agencies

• Decisions would still be made, based on these assessments, by individual regulators to maintain sovereignty of medicines approved for supply in each market
Response: a new, integrated approach

• **International Generic Drug Regulator’s Pilot (IGDRP)**
  – Convergence of specific technical requirements e.g. bioequivalence, biowaivers, selection of foreign reference products
  – Assessment of drug master files and overall report structures so that the evaluations of other regulators can be used in worksharing

• **International Coalition of Medicines Regulators Authorities Generics project** focuses on strategic issues to establish a framework for routinely exchange evaluation reports:
  – Regulator business processes
  – Legal frameworks
  – Secure platforms for sharing confidential information
  – Gap analysis to identify opportunities for generic drugs worksharing that are not already being addressed through existing initiatives

International regulatory cooperation: more important than ever
Pilots for implementation

• Information exchange between regulators on medicines which:
  – have recently received market authorisation, and for which quality and bioequivalence data may be available for sharing (information sharing), or
  – are currently under consideration for market authorisation and may be suitable for worksharing

• TGA involvement in pilot of the EU Decentralised Procedure (DCP) on the evaluation of generic drug applications
  – an application for a marketing authorisation submitted under DCP will be submitted concomitantly to TGA
  – offers applicants the potential to obtain market authorisation in a number of chosen markets as part of a coordinated process
  – Australian registration decision is made by a TGA delegate

• ACSS and TGA-Canada Collaborations
  – successful work/information sharing on four applications with Canada
An ‘Information-sharing’ model
What could these generics initiatives mean for industry?

- More **consistent dossier/product requirements and GMP inspection processes** (through PIC/S and ICMRA) across countries
- **Aligned regulatory interpretation** of requirements on industry
- Worksharing between regulators on aligned submissions **could** provide faster evaluation times and potential for reduced fees to industry
- **Potential for move away from requirement for local reference products** – but will require access to information on the foreign innovator comparator product
- **Enablers for worksharing** may include:
  - greater agreement on biowaivers
  - inventories of patent expirations and anticipated new generics
  - stronger and joined up dialogue with industry
What advice do we seek from industry?

- Input on proposed alignment and worksharing processes
- How to best obtain advice on plans for submissions
- Identification of differences in policy alignment on data exclusivity, legal treatment of generics between countries
- How to address constraints with aligning submissions where:
  - patent expiration dates for the originator product differ between countries
  - different companies have differing commercial rights to particular products in different countries
  - companies plan different market entry times in different countries

International regulatory cooperation: more important than ever
Strengthening international medical devices alignment

- **Confidence building in European Notified bodies** to reduce the number of mandatory application audits

- **International Medical Device Regulators Forum (IMDRF)** program gaining momentum - Australia, Brazil, Canada, China, USA, EU, Japan (and WHO)

- Third party GMP audits institutionalised to satisfy several countries under the **Medical Devices Single Audit Program**
IMDRF program

• Review system for **confidential exchange of information on serious adverse events**, to
  – Better address potentially serious signal detections which have not yet resulted in recalls
  – Develop a rapid communication exchange mechanism and harmonized format for serious recalls
• Implementation of **Unique Device Identification** system
  – Define roadmap to implementing a globally harmonised approach to uniform device identification system
  – Framework for regulators to develop their own UDI systems
• Review of **recognised standards for devices** to increase consistency
Regulated product submission

- Beta testing of standard to make sure it meets business requirements for electronic filing of device applications
- Common, modular table of contents for device applications
- Defining common data elements, structure and electronic format standard to support device identification over product lifecycle

- **Table of Contents divided into 7 different chapters:**
  - Chapter 1 – Regional Administrative
  - Chapter 2 – Submission Context
  - Chapter 3 – Non-Clinical Evidence
  - Chapter 4 – Clinical Evidence
  - Chapter 5 – Labelling and Promotional Material
  - Chapter 6A – QMS Procedures
  - Chapter 6B – QMS Device Specific Information
Software as a (standalone) medical device

- Definitions document finalised and published
- Framework for Risk Categorization to be finalised to introduce foundational approach
- Harmonized vocabulary and considerations for manufacturers, regulators, and users to address unique challenges with SaMD
Medical Devices Single Audit Program

- Develop, manage and oversee a program that will allow single regulatory audit to satisfy needs of multiple regulators
- Improve safety and oversight of medical devices in a more efficient manner while also reducing regulatory burden
- Modelled after Health Canada’s third party program
- Also draws upon best practices and experience of participants
  - USFDA, Health Canada, TGA and Brazil
  - Japan and WHO official observers
Regional responsibilities

International regulatory cooperation: more important than ever
Regional capacity building by TGA/WHO

- Laboratory training (e.g. of staff from PNG and Thailand)
- WHO Western Pacific Regional Alliance for Vaccines Regulation
- Vaccine National Regulatory Authority assessments
- WHO Member State mechanism on SSFFC medical products
- Asia Pacific Leaders Malaria Alliance Regulators’ Group, led by the TGA:
  - improving access to quality medicines and diagnostics
  - helping to contain the spread of artemisinin resistance
  - strengthening capacity to monitor quality of products and to take action when substandard products are detected
Benefits for industry, trade and public health through regional cooperation

- Stronger regulatory convergence in Asian economies facilitates market entry and access to medicines
- Assists regional trade
- Pharmacovigilance information in Asian populations highly relevant for Australia
- Vigilance of counterfeit and substandard medicines coming into Australia
- Control of tropical and subtropical diseases and pandemics in the region
Constraints on collaboration

- Codified processes in regulations can limit flexibility
- Differing financial models and financial resources
- Differences in timing in receiving applications
- Confidentiality issues with sponsors
- Incompatibility of IT systems between regulators
- Different languages and terminology in reports
- Initial increase in cost and work before worksharing is integrated into “business as usual”
- Limited benefits for big regulators
- Staff may see their jobs as being under threat
Different regulators may still reach different conclusions using similar data on overall market authorisation or particular indications.
Some medicines approved in the USA but rejected in Europe after active consideration

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Indication</th>
<th>Year approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Acute myeloid leukaemia</td>
<td>2000 (withdrawn 2010)</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Fibromyalgia</td>
<td>2009</td>
</tr>
<tr>
<td>Ixabepilone</td>
<td>Breast cancer</td>
<td>2008</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>Anti-obesity</td>
<td>2013</td>
</tr>
<tr>
<td>Phentermine / topirimate</td>
<td>Anti-obesity</td>
<td>2013</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Rheumatoid arthritis</td>
<td>2013</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>Homozygous familial hypercholesterolemia</td>
<td>2013</td>
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<tr>
<td>Pirfenidone</td>
<td>Idiopathic pulmonary fibrosis</td>
<td>2010</td>
</tr>
<tr>
<td>Mifamurtide</td>
<td>Osteosarcoma</td>
<td>2009</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Reversal of neuromuscular blockade</td>
<td>2008</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Type 2 diabetes</td>
<td>2007</td>
</tr>
<tr>
<td>Laropirant/ nicotinic acid</td>
<td>Hypercholesterolaemia</td>
<td>2008 (withdrawn 2013)</td>
</tr>
<tr>
<td>Sitaxentan sodium</td>
<td>Pulmonary arterial hypertension</td>
<td>2006 (withdrawn 2010)</td>
</tr>
<tr>
<td>Miglustat</td>
<td>Gaucher disease</td>
<td>2009</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Transdermal patch for libido (women)</td>
<td>2006</td>
</tr>
</tbody>
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Fast track review schemes and provisional/adaptive licensing – will they impact on international collaboration?

• May or may not require full phase III clinical trials to be completed
• Usually based on a direct agreement between one regulator and the sponsor
• Both involve close collaboration with sponsors of trial design and follow up
• This could complicate plans for worksharing

International regulatory cooperation: more important than ever
US and Europe also have very different views on medical device regulation

US FDA Public Report May 2012:

“Unsafe and Ineffective Devices Approved in the EU that were not Approved in the US”

“As shown in this report, the limited testing required in the EU can fail to predict dangerous risks and lack of effectiveness in actual use”
The delicate issue of trust - use of reviews by other regulators....

Confidence building is critical
Back to our top priorities for international cooperation....

Reducing regulatory duplication

Speeding market / patient access to innovative therapeutic goods

Expanding pharmacovigilance reach
How does Australia benchmark with medicines approval times?
Median approval times for NCEs
(total days with regulator plus days with sponsor for responses)

<table>
<thead>
<tr>
<th></th>
<th>All new medicines (NCEs) (2013)</th>
<th>Oncology medicines (2009-13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe (EMA)</td>
<td>478</td>
<td>450</td>
</tr>
<tr>
<td>US (FDA)</td>
<td>304</td>
<td>240</td>
</tr>
<tr>
<td>Japan (PMDA)</td>
<td>342</td>
<td>365</td>
</tr>
<tr>
<td>Australia (TGA)</td>
<td>350</td>
<td>372** (314)**</td>
</tr>
</tbody>
</table>

** Figure for 2011-13; * Jan-Jun 2014 – 314 total days (197 working days with TGA)
But with generic medicines, TGA approvals currently much faster than FDA ones

International regulatory cooperation: more important than ever
Institutionalising greater collaboration

- Need to provide industry with a range of approaches to market authorisation
  - Medicines: Exchange completed evaluations vs worksharing vs full review
  - Devices: Notified body confidence building vs application audit
- Now turning good ideas into practice
  - Generic medicines reviews
  - Medical devices single audit program
  - More joint inspections e.g. of Indian facilities
  - EMA to share orphan drug reports with TGA
  - New wide ranging agreement with US FDA near completion
  - Australia accepted as an assessor in the EU Directorate for Quality of Medicines and Healthcare's procedure for the Certification of Suitability to the monographs of the European Pharmacopoeia
Regulatory convergence and collaboration is the future!

- TGA seen by others as **one of the world’s top 6 medicines regulators** although Australian industry is comparatively small
- International collaboration is more **important for medium sized regulators such as TGA** than for the largest regulators
- **Benefits to Australian/regional industry and for earlier patient access to medicines** if there is stronger regional/Asian capacity and alignment in regulation
- **Several excellent initiatives in place**, but....
  - Some only bilateral or limited in multilateral nature
  - Only cover some steps in the regulatory process
- **Fuller integration of collaboration between regulators into “business as usual”** of regulators will take time