Review Policies for Global Drug Development: Singapore’s Perspective

Dr Christina Lim
Administrator
Health Products Regulation Group
Senior Advisor, International Collaboration
Health Sciences Authority
Singapore

15 April 2008
Outline

• Overview of the Health Sciences Authority
• Biomedical Sciences Initiative
• Regulatory Framework & Review Policies
• Summary
Vision
To be the LEADING INNOVATIVE AUTHORITY
protecting and advancing NATIONAL HEALTH and SAFETY

Mission
- To **wisely regulate** health products
- To **serve** the administration of justice
- To **secure** the nation’s blood supply
- To **safeguard** public health

Health Products Regulation Group • Health Services Group • Applied Sciences Group

A Statutory Board of the Ministry of Health | The Singapore Public Service: Integrity • Service • Excellence
Options for new & greater synergies across Groups

Drugs & Devices
- Product Risk Assessment
- Quality Systems Audit
- Clinical Trials Regulation
- Licensing
- Vigilance & Surveillance
- Enforcement

Health Products Regulation

Health Services
- Blood Banking & Transfusion Services
- Hemovigilance

Applied Sciences
- Health Products
- Quality Analysis

Copyright HSA 2008
Health Products Regulation Group

As of 2 April 2007
Biomedical Sciences Initiative in Singapore
Singapore

- Total Population: 4.48 million (in 2006)
- Singapore Residents: 3.6 million
- Ethnic composition:
  - Chinese: 75.2%
  - Malay: 13.6%
  - Indians: 8.8%
  - Others: 2.4%

Source: Ministry of Health, Singapore
Healthcare Delivery System

• Public healthcare system managed by Government
• Private system provided by GPs & private hospitals
• Primary Healthcare
  • Private GPs (2,000 clinics) : 80%
  • Public outpatient polyclinics (18) : 20%
• Secondary/Tertiary specialist care
  • Private hospitals : 20%
  • Public hospitals/specialist centres : 80%
Public Healthcare Delivery System

- In Apr 2000, all public healthcare institutions were divided into 2 integrated healthcare delivery networks comprising:
  - Hospitals (tertiary and regional)
  - National Specialist Centres
  - Polyclinics

Aim: Greater integration with better quality healthcare services among public sector healthcare providers
Public Healthcare Delivery System

- Institute of Mental Health
- National Skin Centre
- TTSH Medical Centre
- National Neuroscience Institute
- National University Hospital
- Alexandra Hospital
- KK Women’s & Children Hospital
- Changi General Hospital
- Singapore General Hospital
- National Heart Centre
- National Cancer Centre
- National Dental Centre
- Singapore National Eye Centre

Outram Campus
Singapore’s largest concentration of medical facilities & services
Biomedical Sciences Initiative

Government Support & Commitment
Substantial Investment, Long-Term & Coordinated

Industry promotion & facilitation
Public research & manpower training
Strategic investments for developmental & financial returns

Public Hospital Clusters
Regulators
Biomedical Sciences Initiative

► One of the key strategic initiatives in Singapore’s drive towards a knowledge-based, innovation-driven economy

► Strengthening basic research capabilities as it strongly supports clinical research and clinical trials with the necessary capabilities, talent and infrastructure

► Emphasis on Early Phase and ‘Proof of Concept’ studies - key in enabling MNCs to set up dedicated phase I centres to conduct Global Drug Development in Singapore
**Hub for Clinical Trials and Regional Clinical Research Management**

<table>
<thead>
<tr>
<th>Company</th>
<th>Team Size</th>
<th>Bed Capacity</th>
<th>Trial Phases</th>
<th>Additional Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>60-man</td>
<td>41 beds</td>
<td>Phase 1 unit</td>
<td></td>
</tr>
<tr>
<td>GSK Biologicals</td>
<td>25-man</td>
<td></td>
<td>Phase 2-4 trials</td>
<td>GSK Biologicals</td>
</tr>
<tr>
<td>Lilly</td>
<td>60-man</td>
<td>31 beds</td>
<td>Phase 1 unit</td>
<td></td>
</tr>
<tr>
<td>MERCK</td>
<td>Phase 3</td>
<td></td>
<td>Trials</td>
<td>Results used in NDA submission</td>
</tr>
<tr>
<td>Novartis</td>
<td>12-man</td>
<td></td>
<td>Phase 2-3 trials</td>
<td>Centralized data</td>
</tr>
<tr>
<td>Schering-Plough</td>
<td>Phase 2-4</td>
<td></td>
<td>Trials</td>
<td>Data management</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>14-man</td>
<td></td>
<td>Phase 1-4 trials</td>
<td></td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>20-man</td>
<td></td>
<td>Phase 2-4 trials</td>
<td>Data management</td>
</tr>
<tr>
<td>Evershing</td>
<td>Japanese CRO</td>
<td></td>
<td></td>
<td>2nd largest in Japan</td>
</tr>
<tr>
<td>ICON</td>
<td></td>
<td></td>
<td></td>
<td>Clinical Trial Management</td>
</tr>
<tr>
<td>Pharmanet</td>
<td></td>
<td></td>
<td></td>
<td>Clinical Trial Management</td>
</tr>
</tbody>
</table>
CROs in Singapore

- Quintiles Transnational
  - Clinical Trial Management
  - Clinical Trial Supplies
  - Central Lab Services
  - Regional Training

- Covance
  - Clinical Trial Management
  - Central Lab Services

- ICON
  - Clinical Trial Management
  - Central Lab Services

- MDS Pharma Services
  - Clinical Trial Management
  - Central Lab Services

- APEX International Clinical Research Co., Ltd.
  - Taiwanese CRO
  - Large Presence in China

- Eurofins
  - Central lab

- CMIC Pharmaceutical Value Creator
  - Clinical trial management
  - Central Lab Services

- Japanese CRO
  - 2nd largest in Japan

- PPD
  - Clinical Trial Management

- Omnicare Clinical Research
  - Clinical Trial Management
  - Regulatory Affairs Consultation
  - Drug Development Planning

- Pharmanet
  - Clinical Trial Management

- Evergreen System
  - Clinical Trial Management

- Taiwanese CRO
  - Large Presence in China

- Large Presence in China

- Bioequivalence

- Local Start-up Central Lab

- Partnership with LabCorp

Copyright HSA 2008
Growing Base of Drug Discovery

- **60 RSEs**
  - Drug discovery for neurodegenerative diseases
  - Medicinal chemistry

- **40 RSEs**
  - In-vivo pharmacology
  - Target validation

- **20 RSEs; 200 RSEs by 2008**
  - Chemistry process development R&D

- **55 RSEs**
  - Genomics & small molecule technologies-based drug discovery

- **85 RSEs**
  - Drug discovery for TB, Dengue and Malaria

- **62 RSEs**
  - Natural products research for drug discovery

- **15 RSEs**
  - R&D in stem cell expansion

- **80 RSEs (projected)**
  - R&D in biocatalysis

- **15 RSEs by 2008**
  - Drug development for infectious diseases

- **150 RSEs**
  - Oncology biomarker research & genomic data analysis
  - Drug Hunting Teams for cancer and metabolic diseases
  - Integrated computational science research

- **13 RSEs**
  - Neuroscience R&D

- **10 RSEs by 2008**
  - Development of vaccines for infectious diseases prevalent in Asia
Strategic Global Manufacturing Site

Biopharmaceuticals

- >S$1.5 bil, 800 emp
- 3 Chemical Bulk Actives Plants
- Steroids Plant
- Tablet Facility
- Dry Powder Inhalers
- Biologics Fill & Finish
- Chemical Process R&D Centre

- >S$1 bil, 280 emp
- Chemical Bulk Actives Plant
- Tablet Facility
- Tablet Facility Expansion

- >S$1 bil, projected 400 emp
- Formulation Plant

- >S$1.3 bil, 800 emp by 2010
- 5 Chemical Bulk Actives Plants
- Technical Centre
- Chemical Pilot Plant
- Paediatric Vaccines Plant

- S$600 mil, 260 emp
- Chemical Bulk Actives Plant

- S$360 mil, 470 emp
- Infant Formula Plant

- S$190 mil, 140 emp
- Chemical Bulk Actives Plant

- S$210 mil, 100 emp
- Microbial bulk biologics facility

- S$10 mil, 70 emp
- Biologics process devt and contract manufacturer

- S$200 mil, 88 emp
- Antibiotic Intermediates Plant

- S$210 mil, several hundred emp projected
- Nutritional Powder Plant

- S$450 mil, several hundred emp projected
- Antibiotic Intermediates Plant

- Large scale bulk biologics manufacturing
- 1st plant operational by 2010
- 2nd plant operational by 2011
Strategic Global Manufacturing Site
Medical Devices, Research & Clinical Tools Providers

- JMS
  - 500 emp
  - Blood Bag & Catheters

- Siemens
  - 520 emp
  - Hearing Aids

- Affymetrix
  - Projected 140 emp
  - Microarray chips

- BD
  - 800 emp
  - Centre of Competence for Needles & Syringes
  - Critical Care Systems

- CIBA Vision
  - 250 emp
  - Contact Lenses & Global Distribution Centre

- Waters
  - Partnership with Soelectron
  - High performance liquid chromatography systems

- Baxter
  - 1800 emp
  - Large IV Sets, CAPD Solutions, Infusion Pumps

- Biosensors International
  - 180 emp
  - Interventional Cardiology & Critical Care products

- AB Applied Biosystems
  - 130 emp
  - Thermal Cyclers & Sequence Detection System

- PerkinElmer
  - 400 emp
  - Atomic absorption system, Auto liquid dispensing system, Bioassay reader

- Edwards Lifesciences
  - Projected 400 emp
  - Tissue heart valves

- Fisher Scientific International Inc.
  - 90 emp
  - Electrochemistry meters & Thermometry Products

- Fluidigm
  - 18 emp
  - Microfluidic biochips & analysis instrumentation
  - Global Product Devt Ctr for microfluidic biochips & analysis instrumentation
Regulatory Framework & Review Policies
**Biopolis**

**Shared Facilities**
- Shared scientific services and resources (e.g. NMR, flow cytometry, x-ray crystallography, glassware washing, media prep)
- Shared facilities and amenities (e.g. lecture theatres, auditorium, F&B outlets, laundry, childcare, shuttle bus)

**HELIOS**
- Health Sciences Authority
- GSK
- ES Cell Int'l
- RIKEN Office
- British High Comm S&T Office

**NANOS**
- Institute of Bioengineering & Nanotechnology (IBN)
- Johns Hopkins
- Singapore Tissue Network

**MATRIX**
- Bioinformatics Institute
- Science & Engineering Research Council
- Exploit Technologies

**CHROMOS**
- Novartis
- REDI Centre

**CENTROS**
- A*STAR
- BMRC
- EDB BMS Group
- Bio*One Capital
- Bioprocessing Technology Institute

**PROTEOS**
- Institute of Molecular & Cell Biology

**GENOME**
- Genome Institute of Singapore
- Singapore Cancer Syndicate
- Swiss House
Expanding Regulatory Roles

- Controller & Regulator
- Nurturer & Facilitator
- Convenor & Aggregator
Keeping Up with Scientific Developments

- Rapid development in translational research
- Emergence of new products & modalities
  - Biologicals, biotech products, human cell & tissue therapy products, devices, delivery systems, diagnostic products
  - Innovative, complex or combination products
Whole Life-Cycle Approach

Pre-market activities
- Drug/Product design
- Investigational Testing/Clinical Trial
- Product approval for sale
- Product manufacturer

Post-market activities
- Pdt available for sale/supply
- Product purchase/use
Regulatory Framework

► Compliance to International Regulatory Standards
► Rigorous intellectual property framework
► Active promotion of Good Clinical Practice
► New Drug Approval Systems
► Continually enhancing capabilities to manage emerging technologies and therapies
Regulatory Infrastructure Development

- HSA Formed
- BMSI Phase 1
  - S’pore GCP Guidelines
  - Full Route Drug Evaluation
- BMSI Phase 2
  - PICS Membership
  - Enhanced IPR protection
  - Injection of new funding for regulatory capabilities enhancement

## No. of Clinical Trial Certificates

<table>
<thead>
<tr>
<th>Phase</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>21</td>
<td>19</td>
<td>20</td>
<td>24</td>
<td>31</td>
<td>44</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>II</td>
<td>44</td>
<td>50</td>
<td>52</td>
<td>19</td>
<td>49</td>
<td>50</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>III</td>
<td>63</td>
<td>68</td>
<td>97</td>
<td>91</td>
<td>88</td>
<td>90</td>
<td>116</td>
<td>135</td>
</tr>
<tr>
<td>IV</td>
<td>29</td>
<td>28</td>
<td>26</td>
<td>26</td>
<td>32</td>
<td>17</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>165</td>
<td>195</td>
<td>160</td>
<td>200</td>
<td>201</td>
<td>217</td>
<td>253</td>
</tr>
</tbody>
</table>
No. of Approved CT Applications

- Phase I
- Phase II
- Phase III
- Phase IV

No. of Approved CT Applications by Phase (2000-2007)

Copyright HSA 2008

To be the LEADING INNOVATIVE AUTHORITY protecting and advancing NATIONAL HEALTH and SAFETY
Since 2003, three “confidence-based” pathways allow companies to opt for route potentially expediting access to market for new medicine in Singapore

- Full (1998)
  - First-in-world evaluation of innovative products, with focus on innovative therapies for disease predominant in region and those originating from Singapore

- Abridged (Original)
  - Original pathway, following other agency approval

- Verification (2003)
  - ‘Safest’ applications (based on benchmark agency approvals) ➔ quick review and regulatory outcome
Pre-submission consultation

- Product yet to be approved by any regulatory agency
  - Full Evaluation
  - Full evaluation & Regulatory Decision

- Product approved by one drug regulatory agency
  - Abridged Evaluation
  - Abridged evaluation & Regulatory Decision

- Product approved by reference regulatory agencies*
  - Verification
  - Evaluation & Regulatory Decision based on assessment report by benchmark regulatory agency

* Reference regulatory agencies refer to US FDA, Health Canada, UK MHRA, Australian TGA, EU EMEA
NDA: Features of the 3 Evaluation Pathways

- Employs risk-stratification strategy
- Different risk-based evaluation routes take account of product’s international registration status & provides flexibility for companies in planning submissions
- Includes regular review to align with international best practice & meet local needs
- Allows optimal allocation of limited resources
- Dynamic flexibility caters for change in route of evaluation
Risk-based Vigilance

Ongoing vigilance activities to ensure that marketed products continue to be safe.

Process

Risk detection
Monitoring ADRs to detect risks & change in risk/benefit profile

Risk assessment
Assessing risk-benefit profile

Risk minimisation
Minimising risk by appropriate regulatory actions

Risk communication
Communicating information to optimise safe & effective use
Inter-Agency Cooperation covers range of possible activities:
- Harmonisation of regulatory technical requirements
- Exchange of information
- Mutual recognition
- Joint inspection
Summary
Policies for Global Drug Development

- **Wise Regulation**
  Science based & judiciously adapting good international regulatory principles/practices to meet Singapore’s unique situation

- **Regulatory Balance**
  Protecting public health & expediting access to new medicines

- **Increasing Collaboration**
  Strategic Partnership at all levels (local, regional & international) with research institutes, academics, industry & regulatory agencies is key to make process efficient
Finding the Right Balance

Protect Public

Enable & Facilitate

Regulator

Relevant, Responsive & Ready
Thank You

www.hsa.gov.sg