New Drug Development and the Regulatory Environment in Korea

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Clinical Trial Center
1. Overview
Drug Development; ~'70

randomized screening → lead optimization → full development → market
Drug Development; ’70~’90
Drug Development; ‘90~

- High capacity, focused screening
- Lead optimization
- Exploratory development
- Full development
- Market

Target identification & validation

Unmet clinical need = therapeutic target
2. Status of Drug Development in Korea
R&D History of Korean Pharm

“Shift from Generics and IMDs to New Drug Discovery”

216 Pharmaceutical companies: local + international

Vision 2020

“Develop 20 New Drugs & Become Global Top 20 Pharmaceuticals”
<table>
<thead>
<tr>
<th>Products</th>
<th>Sponsor</th>
<th>Status</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics, LB20304a</td>
<td>Local</td>
<td>Approval(USA)</td>
<td>LGLS</td>
</tr>
<tr>
<td>Anticancer, SK 12503R</td>
<td>Gov.</td>
<td>Approval</td>
<td>SK</td>
</tr>
<tr>
<td>Dermatologic, EGF</td>
<td>Gov.</td>
<td>Approval</td>
<td>Daewoong</td>
</tr>
<tr>
<td>Anticancer, DW–116HC</td>
<td>Gov.</td>
<td>Approval</td>
<td>Dong Hwa</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Gov.</td>
<td>Approval</td>
<td>Chung Woi</td>
</tr>
<tr>
<td>Anticancer, DA–125</td>
<td>Gov.</td>
<td>Phase II(Korea)</td>
<td>Dong A</td>
</tr>
<tr>
<td>Hepatitits, G009</td>
<td>Gov.</td>
<td>Phase II(Korea)</td>
<td>Il Yang</td>
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<tr>
<td>Antibiotics, DW–116</td>
<td>Gov.</td>
<td>Phase II(Korea)</td>
<td>Dong Hwa</td>
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<td>Hepatitits, YU–439</td>
<td>Gov.</td>
<td>Phase II(Korea)</td>
<td>Yuhan</td>
</tr>
<tr>
<td>Antibiotics, CFC–222</td>
<td>Gov.</td>
<td>Phase II(Korea)</td>
<td>CJ</td>
</tr>
<tr>
<td>Antidepressants, YKP10A</td>
<td>Local</td>
<td>Phase II(Korea)</td>
<td>SK</td>
</tr>
</tbody>
</table>
# New Drug Exportations

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Partner</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991.1</td>
<td>LGLS</td>
<td>GSK</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>1997.4</td>
<td>Han Mi</td>
<td>Novartis</td>
<td>Anti-Immune</td>
</tr>
<tr>
<td>1997.5</td>
<td>LGLS</td>
<td>SB</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>2000.1</td>
<td>Dong A</td>
<td>Janssen</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>2000.9</td>
<td>Yuhan</td>
<td>SB</td>
<td>Acid blocker</td>
</tr>
<tr>
<td>2000.10</td>
<td>Chong Kun Dang</td>
<td>Alza</td>
<td>Anti-Cancer</td>
</tr>
<tr>
<td>2001.3</td>
<td>Chung Woi</td>
<td>Chugai</td>
<td>Anti-Cancer</td>
</tr>
<tr>
<td>2000.10</td>
<td>LGLS</td>
<td>BioPartners</td>
<td>SR-hGH</td>
</tr>
</tbody>
</table>
Status of Drug Development in Korea

• Strengthen the competitiveness of regulations based on advanced operation of regulation
  • Facilitate early-phase clinical trials
  • Establish comprehensive management system
• Support for infrastructure to conduct world-class clinical trials and designate a regional clinical trial centers
  • 15 designated Regional Clinical Trial Centers
  • Designate 142 clinical trial institutions
• Enhance international cooperation and collaboration among industry, academia and regulatory authority
  • Agreement on mutual cooperation for drug development to facilitate clinical trials in East Asia through the Korea – China – Japan Health Minister Meeting (from 2007)
1987: Establishment of KGCP Guideline as a self-guideline
1990: Accreditation of Clinical Trial Hospitals: 82
1992: New Drug Committee in Central Pharmaceutical Affairs Council (CPAC)
   - Advisory Expert Review for Clinical Protocol/Reports
1993: Governmental Initiatives for KGCP implementation
   - Written Informed Consent, Optional IRB Approval
   - Inspection (Audit) of Clinical Trial
2000: Revision of KGCP - enforcement, 2001. 1
   - Almost identical to the ICH E6 Guideline
2012: Bioethics policy
### Major Changes in New Drug Regulations

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 12, 1999</td>
<td>• Adoption of the Bridging Concept</td>
</tr>
<tr>
<td></td>
<td>- Harmonized to ICH guideline E5</td>
</tr>
<tr>
<td></td>
<td>- Diverse bridging strategies were required</td>
</tr>
<tr>
<td>Jan. 4, 2000</td>
<td>• KGCP Amendment for Harmonizing with ICH GCP</td>
</tr>
<tr>
<td></td>
<td>- Harmonized with ICH guideline E6</td>
</tr>
<tr>
<td></td>
<td>- Protect the rights and safety of subjects</td>
</tr>
<tr>
<td></td>
<td>- Responsibility of investigator</td>
</tr>
<tr>
<td>Dec. 3, 2002</td>
<td>• Introduction of IND System</td>
</tr>
<tr>
<td></td>
<td>- Separation between developmental clinical stage and commercial product approval, such as IND and NDA</td>
</tr>
<tr>
<td></td>
<td>- Participation in international study enabled</td>
</tr>
<tr>
<td>Jun. 30, 2006</td>
<td>• Organization of Clinical management Division</td>
</tr>
<tr>
<td>Jan. 4, 2007</td>
<td>• Introduction of Joint-IRB</td>
</tr>
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</table>
Regional Clinical Trial Centers

- 15 designated Regional Clinical Trial Centers
- US $ 3.5 Million / 5 yrs
- Similar to NIH-GCRC in US [National Institutes of Health – General Clinical Research Centers]
In 2002, IND was Separated from NDA in Korean Regulation

Source: Official Statement of KFDA (Feb. 2012)
Collaborations

Agreement, Partnership & MOU

Regulator, Global Leading Hospital, Global Pharmaceutical Company, Medical Device Company
Where Are We Now?
# SWOT Analysis

## Strengths
- Strong Government’s Leadership
- Ambitious People with well Education
- Strong Basic Science
- Good Medical Infrastructure
- Proven Record in Clinical Development

## Weaknesses
- Language Barrier
- Lack of Continuity
- Limited Experience in Drug Development
- Bueauracracy
- Transparency
- Global Standard

## Opportunities
- Decreasing R&D Productivity
- Financial Crisis
- Open Innovation

## Threats
- Open Competition
- Economic Downturn
- Prioritization
3. R&D Strategy in Korea
R&D Strategy

• Discovery/Research → Development?

• INNOVATION and COLLABORATION
  – To conduct First in Class Research, we need innovative partnership with academia and hospitals
  – To find new druggable targets, new disease & treatment mechanism, we have to collaborate
  – Patient Information and tissue are very important to development of ‘personalized medicine’
  – Specialists
    • Discovery / Research specialists
    • Development specialists
    • Clinical specialists
R&D Strategy in Korea

Sustainable Growth Engine

Establish channel among Academia/ Government/Industry

Build success model of new drug development

Develop specialist group for the future

Entering Global New Drug Development Arena
Scope of New Drug Development in Korea

Basic Scientists

Preclinical Scientists

Pharm. Companies

Clinical Investigators

[Images of logos and organizations related to drug development in Korea]
4. Experiences of New Drug Development in SMC
New Clinical Trials in SMC (Total)

IIT (Investigator Initiated Trial)
SIT (Sponsor Initiated Trial)

Source: SMC e-IRB [2007 ~ 2012]
New Clinical Trials in SMC (by phase)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>234</td>
<td>14</td>
<td>60</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>2009</td>
<td>261</td>
<td>18</td>
<td>78</td>
<td>68</td>
<td>56</td>
</tr>
<tr>
<td>2010</td>
<td>238</td>
<td>19</td>
<td>67</td>
<td>55</td>
<td>56</td>
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<tr>
<td>2011</td>
<td>269</td>
<td>25</td>
<td>75</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>2012</td>
<td>252</td>
<td>20</td>
<td>77</td>
<td>46</td>
<td>46</td>
</tr>
</tbody>
</table>

2008 ~ 2012 SMC IRB, New studies
New Clinical Trials in SMC (by department)

Source: SMC e-IRB [2007 ~ 2012]

<table>
<thead>
<tr>
<th>Department</th>
<th>2012</th>
<th>2007</th>
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</thead>
<tbody>
<tr>
<td>Hematology and Oncology</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>Cardiology</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Radiology</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Pediatrics</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Orthopedics surgery</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Endocrinology and Metabolism</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Laboratory Medicine</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
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<td></td>
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<tr>
<td>Pulmonology</td>
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<td></td>
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<tr>
<td>Surgery</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Obstetrics and Gynecology</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
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</tbody>
</table>
Early Phase Clinical Trials

[First in Human Study]

- **Total of 3 projects**
  - 2010 : 1, 2011 : 2
- **LY287--- Study**
  - Advanced cancer, multi-national
- **Tanibi --- Study**
  - Advanced cancer, new antiangiogenic Ab
- **YH ---- Study**
  - Healthy volunteer, RA

SMC IRB, New studies
SAMSUNG MEDICAL CENTER
as Research Oriented Hospital
CINICAL RESEARCH INSTITUTE
Clinical Research Institute

Clinical Trial Training Center

2003

Research Center for Future Medicine & Opening Academic CRO

2010

3 Government Awards

“Regional Clinical Trial Center”,
“Clinical Trial Professional Training Academy (PI)”
“Medical Device Clinical Trial Center”

by Korean Ministry for Health & Welfare

2008

2011

Samsung Research Institute for Future Medicine
All Phase New Drug Development with SMC

- **Collaboration among Core Facilities**
  - CRI, T-CRO (Translational Clinical Research Operation) with Clinical Data Warehouse
  - Animal Lab, Tissue Bank, Genomic Research Institute, Molecular Imaging Center, etc.
Hunter syndrome

- Genetic disease associated with X-chromosome
- Mucopolysaccharidoses, MPS type II
- Metabolic syndrome with accumulation of heparan sulfate, dermatan sulfate etc.
- Mental & physical retardation, early death (10~15 years)
- Incidence: 1 / 100,000 ~ 150,000 male
- "Elaprase™": Unique & exclusive drug, very expensive
Paradigm Shift in Drug Development

<table>
<thead>
<tr>
<th>Shift away from primary care blockbuster model</th>
<th>Towards targeting more niche patient populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Long expensive R&amp;D process costing on average $1bn</td>
<td>▪ Faster and often cheaper R&amp;D process allowing a greater time at market</td>
</tr>
<tr>
<td>▪ Competition from me-too and generic drugs</td>
<td>▪ Smaller sales forces required</td>
</tr>
<tr>
<td>▪ Most drugs only work in approximately 50% of patients</td>
<td>▪ Orphan drugs receive incentives such as market exclusivity, tax and fee reductions and regulatory assistance</td>
</tr>
<tr>
<td>▪ Risk of side effects and pharmacovigilance issues</td>
<td>▪ Greater focus on “specialty” pharma and personalized medicines targeting small patient populations with high value drugs</td>
</tr>
</tbody>
</table>

DataMonitor “Orphan Drug Trends 2011 (Nov. 2011)
Examples of New Drug Development

- Animal model development, leads compound production, etc
- Research fund from government for candidate discovery, 2002~2007

2000

- Pilot production/processing
- Preclinical model establishment

2008

- Cell line
- Patent
- Toxicology
- Commercial Scale Production
- Research fund from government for preclinical study, 2009~2011

2009

- Approval: Phase ½ study
- Research fund from government for clinical study, 2010~2012

2010

- Finished phase ½ study
  - WHO-INN
  - Orphan drug
  - KFDA NDA submission

2011

- KFDA Approval
- Global Export

2012

Hunterase™
Factors

- Market driven
- Patients Relation
- Cooperation
- Science based
- Passion
Players of Drug Development

SMC

Clinical Research Institute

GREEN CROSS

SMC Investigators
Towards The Global Drug Development

- Networking
- Open innovation
- Collaboration
감사합니다！
感謝！
Thanks！