RECENT DEVELOPMENT OF INNOVATIVE DRUG R&D IN CHINA

Prof. SANG Guowei

President, Chinese Pharmaceutical Association

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Outline

1. Rapid Growth of Chinese Pharma Industry & Market
2. Considerations for China Bio-Pharma Innovative R&D Strategy
3. Examples of Innovative Drug R&D in China
4. Future Perspectives of the Chinese Pharma Industry
Rapid Growth of Chinese Pharma Industry & Market

Chinese Pharmaceutical Industry Grows Rapidly, Benefiting from Economic Development and Favorable Policy

- National income increases
- Population aging brings along more healthcare demand
- Urbanization boosts healthcare consumption
- New healthcare reform leads to an era of universal health coverage
- Important measure to improve people's livelihood and stimulate domestic demand

In the past five years, average annual increase rate is 20.1%
The “Development Outline for Bio-Industry” issued by the State Council (Jan. 2013) clearly stated the goal to develop bio-industry to become one of the pillar industries of the nation’s economy by 2020.

- During 2013 – 2015, the annual growth rate for bio-industry is expected to be 20%.
- By 2015, the value of the national bio-industry output is expected to reach 4 trillion RMB Yuan (around 7% of GDP).
- By 2020, bio-industry is expected to become one of the pillar industries in China.
CSPC PHARMACEUTICAL GROUP: R&D Investment Increases Year by Year

- New technical innovation to support the development of CSPC
- Achieved the strategic transformation from “raw materials to formulations and from generic drugs to innovative drugs”, with annually increased proportion of R&D investment
- The sales of Class I drug Butylphthalide Series are expected to exceed one billion RMB Yuan in 2013
- Products such as Butylphthalide, Levoamlodipine Maleate, Oxiracetam and PEG-rhG-CSF, all supported by government funds, have become a new growth engine for CSPC
Principle of Early Assessment / Early Elimination
(Fail Early, Fail Cheaply)

- **Hepatotoxicity**
  - Human liver cell line
  - Biliary excretion
  - Mitochondrial toxicity
  - P450 induction

- **Cardiotoxicity**
  - hERG Screening
  - CLIP panel
    (Myocardial channel)

- **Renal toxicity**
  - Cell lines
  - Transgenic mice

- **Common methods**
  - Biomarker
  - *In vitro* model
  - Image analysis
  - Animal model

- **Pathology and clinical pharmacology monitoring**
  (Sub-acute studies)
Analysis of Crystal Structure of 5-serotonin Receptor Subtypes 1B & 2B

• Demonstrated the receptor subtype specificity and signal transduction mechanism, the receptor and the ligand recognition and regulatory mechanism
• Provided structural model for drug design
• Provided guidance on the anti-migraine and anti-obesity drug development
• This was the first time for the Chinese scientists to publish papers on GPCR crystal structure

Analysis of Crystal Structure of Human Glucagon Receptor (GR)

• By using the innovative technology of the thermokinetics and receptor fusion, the first crystal structure of GPCR subtype B, anti-diabetes drug target, has been successfully analyzed
• This was the second milestone of GPCR structural biology research, providing the guidance on the analysis of the crystal structure of GPCR subtype B, leading the new wave of research of GPCR structure and function
The Potential Drug Target in Osteoporosis Treatment: CKIP-1

- The regulatory mechanism of bone formation was systematically studied. The new proteins of CKIP-1 with specific regulatory function were discovered, possible candidate targets for the treatment of osteoporosis.
- It provides a new therapeutic approach for osteoporosis based on bone formation. It has taken a solid step forward on osteoporosis treatment to solve the difficult medical problem of not being able to make up for loss of bone mass.
- It is the first nucleic acid delivery system in the world for specific targeting osteoblast.
Following the inspection from Sweden and Belgium in March 2012, received OECD GLP Compliance Statement, without any significant audit findings.

In April 2013, became the first safety assessment organization in China to pass the GLP laboratory project audit by the British Medicines and Healthcare Products Regulatory Agency (MHRA).

<table>
<thead>
<tr>
<th>Safety assessment project (2011-)</th>
<th>Domestic projects</th>
<th>Overseas projects</th>
<th>Chemical drug, Traditional Chinese medicine, Biological drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>166 Drug test times</td>
<td>135 Drug test times</td>
<td>31 Drug test times</td>
<td>PK/PD: 18; SP: 1; MTD/DRF/Tox: 12</td>
</tr>
<tr>
<td>All safety assessment project</td>
<td></td>
<td></td>
<td>All are primate species, including one obtaining British MHRA approval for clinical trial; one submitted to US FDA</td>
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</tbody>
</table>
The Chinese National Compound Library: The Largest in Asia

• Supported by the former Ministry of Health, Ministry of Science & Technology, Chinese Academy of Sciences and Shanghai Municipality, the Chinese National Compound Library constructed a state-of-the-art facility (6,300 m²) specialized in sample storage, expansion and application. Operation started at the beginning of 2012.

• Current capacity: 1.73 million compounds of diversified structures, the largest in Asia.

• Managed by novel organizational mechanisms and presently running smoothly. In 2013, it provided 257,300 compounds to 37 research groups and conducted numerous high-throughput screening campaigns covering 1,331,800 samples.
Chinese Vaccine Regulatory System Passed WHO Assessment (2011)

National Institutes for Food & Drug Control were responsible for two functions:

Function 3: Vaccine batch release 100% pass
Function 4: Integrated laboratory 100% pass

- The Chinese vaccine regulatory level meets the international standards
- Established the basis for the Chinese vaccine industry to compete in the international market
China National Science and Technology Major Project

Medium and Long-term Scientific and Technological Development Plan (2006-2020)

2006-2010  2010-2015  2016-2020  2021 - · · ·

Science and Technology Major Project

Major New Drug Innovation and Development
- New drugs, Large-scale products
- Technology platform, innovation capability

Infectious Disease Prevention and Control
- Technology, plan, strategy and product
- Platform network, emergency response

Strategic emerging industry
- Provide support for protecting people’s livelihood and development of pharmaceutical industry

Down-stream innovation chain industrial application oriented
Key Tasks of the New Drug Innovation and Development Major Project

- Innovative drug discovery and development
- Transformation of pharma technologies
- Technological platforms for innovative drug R&D
- Construction of new drug incubator bases
- Key technology research for new drug R&D
## 2008-2013 New Drug Development in 10 Major Therapeutic Areas in China

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Total</th>
<th>Phase III clinical trial</th>
<th>New drug certificate granted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Chemical drug</td>
<td>Tradition-al Chinese medicine</td>
</tr>
<tr>
<td>Antineoplastic drug</td>
<td>21</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular disease drug</td>
<td>33</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Neurodegenerative disease drug</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes drug</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Anti-psychotic drug</td>
<td>8</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune disease drug</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Anti-infectious (drug-resistant) drug-resistant drug</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anti-TB drug</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anti-viral drug</td>
<td>20</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>45</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
<td>42</td>
<td>20</td>
</tr>
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</table>
Examples of Innovative Drug R&D in China

Positive Progress in Drug Development

By September 2013, 74 New Drug Certificates were awarded for 52 compounds (including 33 compounds and 44 certificates awarded during the “11th Five-Year” period), of which independent intellectual property right has been granted for 36 compounds (69%)
Small Molecular Targeted Oncology Drug – Icotinib Hydrochloride

- The new generation small molecular targeted anti-cancer drug, which targeted at epidermal growth factor (EGFR) tyrosine kinase
- With completely independent intellectual property rights
- Indicated for advanced non-small cell lung cancer
- Phase III clinical study showed that the median progression-free durations were 137 days in Icotinib hydrochloride group, and 102 days in Gefitinib control group, respectively; the median progression durations were 154 days in Icotinib hydrochloride group, and 109 days in Gefitinib control group, respectively

ICOGEN trial design

- Age: 18-75y
- IIIB/III grade NSCLC
- Expect Survival Time ≥12w
- After 1 or 2 chemotherapy (one cis platin or carboplatin)
- PS score ≤ 2
- RECIST target lesion (at least one)
- Randomly 1:1

<table>
<thead>
<tr>
<th>PFS</th>
<th>OS</th>
<th>ORR</th>
<th>DCR</th>
<th>TTP</th>
<th>HRQoL</th>
<th>Safety/Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icotinib 125 mg Tid</td>
<td>Gefitinib 250 mg Qd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dicycloplatin contains 4 hydrogen bonds with a cage-like structure, which can be dissociated by helicase of tumor cells, allowing targeted release of carboplatin.

- The objective response rates of dicycloplatin / paclitaxel and carboplatin / paclitaxel for first-line treatment of advanced non-small cell lung cancer were 36.44% and 30.51% respectively. The disease control rates (CR + PR + SD) were 85.59% and 80.51% respectively, with dicycloplatin group being higher.

- Subgroup analysis showed that for patients with stage IV NSCLC, the disease control rates of dicycloplatin and carboplatin treatment group were 86.42% and 77.78%, respectively with dicycloplatin being significantly superior ($p = 0.0155$)

- Dicycloplatin / paclitaxel is a safe and effective treatment regimen for advanced non-small cell lung cancer, its efficacy is similar to or superior to carboplatin /paclitaxel.
Class 1 Drug New Quinolones – Antofloxacin Hydrochloride

- The first fluoroquinolone with independent intellectual property rights in China; the first marketed Class 1.1 chemical new drug supported by funding from the Major Project
- The half-life is up to 20 hours, with superior clinical efficacy and safety than levofloxacin
- New Drug Certificate was granted in April 2009
- Received China International Industry Fair Innovation Award in 2009
- Launched in 2010
Drug Name: Peramivir Trihydrate Sodium Chloride Injection

Formulation: Injection

Strength: 100ml: peramivir trihydrate (C\textsubscript{15}H\textsubscript{28}N\textsubscript{4}O\textsubscript{4}) 0.3g and sodium chloride 0.9g

Indication: Influenza A in adults

Launch time: April 2013, H20130016

Patent: ZL200710143607.5

- **High dose** group is non-inferior compared with oseltamivir phosphate

- **Low dose** group is superior compared with oseltamivir phosphate
Butylphthalide

- Butylphthalide has the **dual functions** of **microcirculation reconstruction** and **mitochondria protection**, and **increases brain blood perfusion** in the ischemic area in patients with cerebral infarction, cerebral thrombosis or stroke.

- Butylphthalide is the first Class I new drug in China indicated in cerebrovascular disease, with independent intellectual property rights including eight national patents and two international PCT patents.

- Annual sales was over 1 billion RMB Yuan in 2012.
Class 1 Anti-Inflammatory New Drug – Imrecoxib

- The first selective cyclooxygenase-2 (COX-2) inhibitor in China
- Integrated research of structural biology, computational chemistry, medicinal chemistry and other disciplines
- An innovative drug by applying the new concept of “moderate inhibition” in the drug design and optimization
Nimotuzumab

- IgG1 subtype, molecular weight 150 Kda
- containing human antibody frameworks and murine CDRs sequences
- expressed in NS0 cells
- IV formulation, 50mg:10mL
- Recommended for treatment of head and neck tumors in NCCN Guideline (2009 edition)

2005  2008  2013

New Drug Certificate  Manufacturing Approval Number  Re-registration
Class 1 Biotechnological New Drug – Recombinant Human Pro-Urokinase (rhPro-UK)

- 12 patents awarded
- Indicated for the treatment of thrombosis, with similar effect compared with imported drug of the same class, but with better safety profile (mortality rate of Pro-UK treatment of AMI was only 2%, only one intracranial hemorrhage case in total 225 treated patients)
- New Drug Certificate and manufacturing license has been granted. Fermentation broth production line with an annual output of 40,000 liters has been set up. The price is expected to be about 5000 RMB Yuan/person, which is only one half of that of imported TPA thrombolytic drug.
Conbercept Ophthalmic Injection (KH902)

- The core region of Conbercept was formed by human VEGFR1 IgG-like area 2, VEGFR2 IgG-like areas 3, 4 and human IgG Fc.
- Fully humanized amino acid sequence
- High affinity, can bind with VEGF more closely than natural receptors or monoclonal antibody
- Block all VEGF subtypes and PIGF
- Completely penetration into the retina to improve macular degeneration
New Anti-Viral Drug for Hemorrhagic Fever with Renal Syndrome – A Monoclonal Antibody

- Class 1 biological product. It has been approved and marketed.
- Phase III clinical trial conclusion: “anti-hemorrhagic fever with renal syndrome virus monoclonal antibody injection” is for the treatment of patients with hemorrhagic fever with renal syndrome, with good safety profile and demonstrated efficacy, and superior to conventional drug therapy.
Recombinant Humanized Anti-CD25 Monoclonal Antibody (Daclizumab)

- Humanized antibody structure, expression in CHO cells
- Effectively blocks the IL-2 pathway, clinically used for inhibition of rejection after organ transplantation

Graft rejection: makes the situation of organ source shortage even more challenge
Encephalitis B Attenuated Live Vaccine – Passed WHO Pre-qualification

- Co-developed by the National Institutes for Food & Drug Control and Chengdu Institute of Biological Products
- Class 1 new drug
- The seed of encephalitis B attenuated live vaccine and its manufacturing process was independently developed with intellectual property rights
- Won the top award of National Science and Technology Progress
- The WHO Standardization Committee has based on China’s manufacturing process and testing procedure of encephalitis B attenuated live vaccine to establish WHO procedure (TRS910)
- Passed WHO pre-qualification
Recombinant Hepatitis E Vaccine

1998
E2 (pORF2)

2001.10
Antigen 239

1998
Antigen design/engineering

2002.12
Lab-scale

2003.07
Pilot-scale

2007.01
Phase III lots

2013
Approval

Process optimization / scale-up

Key technologies

• Escheriehia coli Expression System
• VLPs

The world’s first vaccine for the prevention of hepatitis E
The Sabin Anti-polio Inactivated Vaccine

- Home-grown R&D; production using attenuated strain; technology of more safety
- Avoid to induce vaccine related cases from OPV and other cases from vaccine derived virus.
- We took the lead internationally in clinical trials. The vaccine had a good safety profile. The positive conversion rate was 100%. The antibody level was higher than imported vaccine and OPV vaccine. The vaccine can provide protection for all kinds of wild type strain virus.
- The purity and potency of the antigen were accepted by WHO
Completed phase III clinical trials of EV71 vaccine involving more than 30,000 children under 5 years old. Results showed that the vaccine has good safety and efficacy profiles in infants. (The preventive effects of vaccines manufactured by three manufacturers were all higher than 80%)
TCM Injection Against Cerebral Ischemia – Salvianolate for Injection

**Significant clinical efficacy**

**Significant cerebrovascular effect**

- Improve cerebral blood flow without vein steal, does not affect the peripheral blood  
  ![Graph](image1)
- Moderate increase in brain metabolism  
  ![Graph](image2)
- Inhibition of the main risk factors (calcium, free radicals and excitotoxicity) for the brain damage  
  ![Graph](image3)
- Stimulate neurogenesis and brain angiogenesis  
  ![Graph](image4)
- Effect on anti-platelet aggregation and antithrombotic  
  ![Graph](image5)
- Some anti-inflammatory effect  
  ![Graph](image6)
- Can penetrate through the **blood-brain barrier**  
  ![Graph](image7)
Future Perspectives of the Chinese Pharma Industry

Common Applied Technology and Focus for Biologic Products

- New vaccine, adjuvant, therapeutic vaccines
- Antibodies - small molecule drug conjugates (ADC), bifunctional antibodies
- Stem cells (off-the-shelf) treatment
- Synthetic biotechnologies and products
- Biological drug intake and release technologies
- Recombinant coagulation factor
- International cooperation platform for quality standards of antibodies and biosimilars
Future Perspectives of the Chinese Pharma Industry for Chemical New Drug

• Antineoplastic drug
  Target and immune therapy (WNT, PI3K-AKT-mTOR, c-MET, PD1, PD-L1, CTLA4, α1A-AR, PARP inhibitor)
• Cardiovascular disease drug
• Neurodegenerative disease drug (Aβ, DC20)
• Diabetes drug (PCSK9, SGLT2)
• Anti-psychotic drug (BACE, AMPA)
• Autoimmune disease drug (SYK)
• Anti-infectious (drug-resistant)
• Anti-TB drug
• Anti-viral drug
Levels and Stages of Innovative Drug R&D in China

- **Generic drugs**
  To solve the issue of accessibility

- **Follow-on innovation** based on the original targets
  (me-too, me-better)

- **Innovation of new target therapies and new structure drugs**
  To address medical needs and provide new treatment options

From the survey on the registration applications of Class 1.1 drugs, it is concluded that the main innovation R&D activities in China are still at the first and second levels. The R&D level is at the transforming stage from mainly generics to both innovation and generics.
Pharmaceutical companies
- Design and production of drugs
- Design and production of prognostic and diagnostic reagents

Laboratory
- Analysis of various groups for target identification
- Preclinical models
- Analysis of clinical samples

Clinical hospital
- Disease phenotype
- Clinical trials
- Sample collection

Data integration
- Molecular markers
- Disease biomarkers
- Drug target

- Rational drug design
- More effective therapeutic drugs
- Personalized treatment

Translational research cycle - laboratory bench researchers, clinicians and pharmaceutical companies, all must well cooperate to design more reasonable drugs to improve the therapeutic effect.
Future Perspectives of Biopharma R&D in China

The overall objective of the “New Drug Innovation and Development Major Project” is to develop China to a country with a large pharmaceutical industry with strong science and technology capabilities by 2020, in order to meet the needs of protecting the health of Chinese people, safeguarding the national strategic security and social stability.
Thank You!