Taiwan Biotech and Partnering with China Companies

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1. Current Status of Taiwan’s Biotech Industry

Taiwan is an island state of 23.2 million people residing on a land area of 35,980 square kilometers (13,892 square miles), which is slightly smaller than the combined areas of Maryland and Delaware of the United States. Over 99.9% of the population is covered by the National Health Insurance, with a total healthcare spending of US$ 30.3 billion (6.6% of GDP, in comparison to 17.6% and 5.1% for USA and China, respectively). The life expectancies for males and females in Taiwan are 76 and 83 years, respectively. Other major healthcare indicators of Taiwan include: 1.7 physicians per 1,000 people (USA, 2.4; China, 1.4) and 6.9 hospital beds per 1,000 people (USA, 3.1; China, 4.2).

Taiwan’s biotech industry can be divided into three major categories: applied biotech, pharmaceutical and medical device, with about equal numbers of companies (400) for applied biotech and pharmaceutical, and over 600 companies for medical device (Table 1). As of September, 2012, there are 23 bio-industry related companies on Taiwan’s stock exchange market, 46 on OTC market, and 37 preparing for IPO. The total revenue of Taiwan’s biotech industry was US$ 8.15 billion in 2011, with domestic sales accounting for four fifths of total revenues of companies in the pharmaceutical category, and three fifths in the applied biotech, as well as the medical device category (Table 1).

Table 1. Status of Taiwan’s Biotech Industry (2011)

<table>
<thead>
<tr>
<th>Industry Sectors</th>
<th>Applied Biotech</th>
<th>Pharmaceutical</th>
<th>Medical Device</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revenue (US$ Billion)</td>
<td>2.27</td>
<td>2.51</td>
<td>3.37</td>
<td>8.15</td>
</tr>
<tr>
<td>Company (No.)</td>
<td>402</td>
<td>400</td>
<td>626</td>
<td>1,428</td>
</tr>
<tr>
<td>Workforce (No.)</td>
<td>10,875</td>
<td>19,332</td>
<td>30,250</td>
<td>60,457</td>
</tr>
<tr>
<td>Export value (US$ Billion)</td>
<td>0.92</td>
<td>0.54</td>
<td>1.39</td>
<td>2.85</td>
</tr>
<tr>
<td>Import value (US$ Billion)</td>
<td>1.16</td>
<td>2.91</td>
<td>1.86</td>
<td>5.93</td>
</tr>
<tr>
<td>Domestic sales vs. Export</td>
<td>60:40</td>
<td>78:22</td>
<td>59:41</td>
<td>65:35</td>
</tr>
<tr>
<td>Domestic market (US$ Billion)</td>
<td>2.51</td>
<td>4.88</td>
<td>3.84</td>
<td>11.23</td>
</tr>
</tbody>
</table>

Source: Biotechnology and Pharmaceutical Industries Promotion Office, MOEA, 2012

In view of the long, complex, risky, and costly process for drug development, the Taiwan government has implemented the National Research Program for Biopharmaceuticals (NRPB) to support the development of new therapeutics for disease prevention, diagnosis, and treatment. It is
a 6-year program (2011-2016) with a total funding of US$ 540 M, covering all stages of drug R&D from discovery research to preclinical and clinical developments. Concerted efforts by universities, hospitals, research institutes and the industry are organized under specific clinical study consortia for hepatoma, lung cancer, etc. The various research areas and functional groups of NRPB are shown in Figure 1.

**Figure 1. NRPB Research Areas and Functional Groups**
2. Drug Innovation Capability of Taiwan

Taiwan’s pharmaceutical industry was based primarily on generic drugs, and prior to year 2000, core capabilities for the development and manufacture of generic drugs had been largely established. However, due to frequent drug price-cutting by the Bureau of National Health Insurance, export restrictions by foreign countries, limiting size of the domestic market and fierce competition among local manufacturers, it has become increasingly difficult for domestic companies to further expand market and increase profitability of generic drugs. This has led to a shift in R&D focuses from generic drugs to new drugs by Taiwan’s companies and research institutes. Solid results from the decade-long effort on drug innovation are beginning to show up, as illustrated by several out-licensing deals with global pharmas (Table 2) over the last few years. Furthermore, remarkable successes are also exemplified by recent domestic launches, such as Suile® (速癒樂®) by Hedonist Biochemical Technologies Co. Ltd (友合生化), LipoCol Forte (壽美降脂一號) by NatureWise Biotech & Medicals Corp. (彥臣生技), PG2 (懷特血寶) by PhytoHealth Corp. (懷特生技), bendamustine by Innopharmax (因華生技) and MS-20 by Microbio (中天生技).

Table 2. Out-Licensing Deals of Drugs Innovated in Taiwan

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Taiwan Company</th>
<th>Indication</th>
<th>Licensee, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myozyme</td>
<td>Synpac: US Subsidiary of CSRC (中橡)</td>
<td>Pompe Disease</td>
<td>Genzyme, 2000</td>
</tr>
<tr>
<td>Antibody 168</td>
<td>AbGenomics (台醫生技)</td>
<td>Autoimmune Disease</td>
<td>Boehringer Ingelheim, 2005</td>
</tr>
<tr>
<td>TuNEX</td>
<td>Mycenax (永昕)</td>
<td>Rheumatoid Arthritis</td>
<td>Bio A&amp;D, South Korea, 2007</td>
</tr>
<tr>
<td>GNX-8</td>
<td>Glyconex Inc. (台灣醣聯)</td>
<td>Colon Cancer</td>
<td>Otsuka Pharm (大塚製藥), 2008</td>
</tr>
<tr>
<td>Anti-IL20 MAb</td>
<td>National Cheng Kung University (成大張明熙教授)</td>
<td>Osteoporosis</td>
<td>Novo Nordisk, 2012</td>
</tr>
</tbody>
</table>

Source: ITIS Program, Development Center for Biotechnology, Taiwan

Discovery research and preclinical development in academia including universities and research institutes play increasingly important roles in Taiwan’s drug development value-chain. A prime example was Myozyme® (alglucosidase alfa), developed by Distinguished Research Fellow - Dr. Yuan-Tsong Chen (陳垣崇) of Academia Sinica (中央研究院), for the treatment of Pompe Disease. Another example was Anti-CemX, innovated by Distinguished Research Fellow - Dr. Tse Wen Chang (張子文) of Academia Sinica (中央研究院), and licensed to Fountain Biopharma (泉盛生技).
- a subsidiary of Microbio (中天生技). It is a second generation antibody therapeutic following the asthma drug Xolair (omalizumab, launched by Tanox in 2003, 2010 revenues US$ 369 M for Novartis, US$ 616 M for Genentech/Roche), which directly blocks immunoglobulin E. The diabetic foot ulcer drug candidate **ON101 (DCB-WH1)** is a botanical new drug innovated at Development Center for Biotechnology (DCB) and transferred to Oneness Biotech (合一生技) - a subsidiary of Microbio (中天生技). It is the first new drug candidate innovated in Taiwan that has entered phase III clinical trials. In addition, **LT-Hib**, an injection vaccine against Haemophilus Influenzae type B based on a novel vaccine adjuvant (LT) invented by researchers at DCB, has been licensed to a domestic company Tuckmore Biotechnology (桐核麥), and is now in phase I clinical trials. A protein drug derived from genetically mutated snake venom as an **αβ3 Integrin antagonist** by researchers at National Taiwan University and National Cheng Kung University was recently licensed to Twi Biotechnology, Inc. (安成生技).

There are currently 85 cases of clinical trials sponsored by Taiwan companies for new drugs (including: new active ingredients, new indications, new formulations, new efficacious recipes, new treatment routes, and new biological products), with 45 (52%) for clinical phase II trials (44 in Taiwan and one in USA), 19 (22%) for clinical phase I trials, 21 (25%) for phase III trials, and one (1%) for NDA. Among these, 44 had been approved by US FDA for clinical studies, with 24 for phase II trials (**Figure 2**).
Figure 2. New Drug Development Status of Taiwan

a. Classification of new drugs

b. IND applications

c. Clinical stages of new drug development
3. Partnering of Taiwan Companies with Global Pharmas

Taiwan’s biotech companies have been active in forming alliances with international companies, exploring contract manufacturing opportunities and laying out overseas sales channels. Furthermore, as of September 2012, 44 domestic manufacturers of Taiwan have passed the PIC/S GMP examinations. And beginning on Jan. 1, 2013, ahead of Korea and Japan, Taiwan will become a member of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S). This should help attract global pharmas and investors to Taiwan for factory construction and contract manufacturing, and thereby strengthen international competitiveness of the industry. The long-term efforts on the internationalization of drug manufacturing standards have begun to pay off, as evidenced by the compound annual growth rates of 15.2% and 14.3%, respectively for API and western drugs during 2007~2011.

Currently, the main business model for partnership between Taiwan drug companies and global pharmas is based on in-licensing for preclinical or early clinical development in Taiwan, followed by out-licensing to international pharmas for late clinical development abroad. Several cases of new drug development are cited as examples in the following.

(1) **PG2**: a botanical new drug that PhytoHealth Corp. (懷特生技) licensed in from Pharmagenesis in 1999, and licensed out to EcoPharm in 2007. It is now under phase II clinical trials.

(2) **PEP02**: a nano-liposome formulation of camptothecin (nanoliposomal irinotecan) that PharmaEngine Inc (智擎生技) licensed in from Hermes BioSciences, USA in 2003. After completion of phase II clinical testing in 2011, exclusive development and commercial rights were licensed out to Merrimack Pharmaceuticals, USA. In the deal, PharmaEngine received US$ 10 million as upfront, and will receive US$ 210 million as milestones, plus royalties for revenues in Europe and Asia, while Merrimack covers development costs in the licensed areas. PharmaEngine retains exclusive development and commercial rights in Taiwan.

(3) **Nephoxil (PBF1681)**: a new drug for kidney diseases that Panion & BF Biotech (寶齡富錦) licensed in from Michigan University in 2001 for development. In 2005, the USA rights were licensed out to, Keryx, USA, and in 2007 the Japanese market right was licensed out to a Japanese company - JT, and its subsidiary - Torii. It is now under phase III trials in USA and Japan.

(4) **Nemonoxacin**: an antibiotic that TaiGen Biotechnology Co., Ltd. (太景生技) licensed in from P&G in 2005. After completing repeat-dose phase I clinical trials, and phase II clinical trials approved by US FDA for two indications: community-acquired pneumonia and diabetic foot
infections in 2010, TaiGen signed an agreement with Warner Chilcott in Ireland for development and
marketing rights in Europe and North America. In December, 2011, Warner Chilcott announced
that it will transfer exclusive world rights for late stage clinical development, manufacture,
commercialization and sub-licensing rights back to TaiGen. It is now in Phase III clinical trials in
Taiwan.

(5) TMB-355: an antibody against HIV that TaiMed Biologics (中裕新藥) - a reinvestment of
Microbio (中天生技), licensed in from Genentech in 2007. It was approved in November, 2010 by
injection has also been approved by US FDA for phase I clinical trials. Furthermore, TMB USA - a
subsidiary of TaiMed Biologics (中裕新藥), has licensed in an antibody fusion technology from
Rockefeller University and used it to improve the efficacy (> 200 folds) and blood retention time of
TMB-355, greatly increasing its potentials for the treatment and prevention of AIDS.

Other recent partnerships of Taiwan companies with global pharmas are briefly described below.
Medigen Biotechnology (基亞生技) signed a licensing MOU with Il-Yang Pharm - the second
largest pharmaceutical company in South Korea - for an H5N1 flu vaccine. Mycenax Biotech (永
昕) and MACTER signed a contract for sales of its TuNEX products to countries in the Middle East
and Southeast Asia, including Pakistan, Jordan and Lebanon. Sinphar (杏輝) subsidiary SinGuo
Biotech (杏國生技) licensed in Veregen, an herbal medicine for the treatment of anal and genital
warts, from MediGene in Germany, coupled with raw material supply contract for the Taiwan market.
Glyconex Inc. (台灣醣聯) and Japan's Mitsubishi Gas Chemical (三菱瓦斯化學) signed an
agreement to build antibody manufacturing facility in Japan for contract manufacturing of cancer
and immune drugs. The Animal Technology Institute Taiwan (ATIT) and Bayer AG are jointly
developing a single dose vaccine for pig mycoplasma. Abnova (亞諾法) and GSP in Japan will
jointly launch a new product based on fluorescence in situ hybridization (FISH) for detection of
gene amplification and translocation. In addition, Abnova is collaborating with BioTek
Instruments in the US on a technology platform (Interactor®) for screening inhibitors of
protein-protein interaction.
4. Cross-Strait Collaboration and Taiwan Biotech Companies in China

China's booming pharmaceutical market - ranked by IMS Health as 9th in the world in 2005, 3rd in 2010, and projected to 2nd in 2016, just after USA - has drawn great attentions from global pharma. The biotech drug industries of Taiwan and China can be said to complement each other, in view of the former’s track records in drug innovation, IP protection, clinical research, international GXP compliances, regulatory transparency and market experience in China, and the latter’s huge market with fast growing economy, strong government support, abundant resources and raw material supplies, and relatively low production costs.

A Cross-strait Cooperation Agreement on Medicine and Public Health Affairs (海峽兩岸醫藥衛生合作協議) was signed in December, 2010, based on the Economic Cooperation Framework Agreement (ECFA) between Taiwan and China. Clear objectives for the cross-strait collaboration on new drug development have been specified:  (1) to establish a cooperation mechanism for GLP, GCP, and GMP inspections; (2) to actively promote the harmonization and coordination of technical standards and regulations based on universally recognized standards (such as ICH) for product safety; (3) to reduce repetition of clinical trials - specifically, approved institutes and trial projects conforming to GCP guidelines will be of high priority to be enlisted for clinical research cooperation, whereby both parties will study the possibilities of accepting each other’s trial results.

The main business strategies for Taiwan companies in China can be summed up as: (1) formation of affiliated companies for product launch, production site, R&D Center and market development; (2) R&D collaboration.

Regarding product launch, affiliated companies in China set up by Taiwan companies are cited below. (1) SCCPC (蘇州中化) by CCPC (中化製藥): over 40 products listed in National Medical Insurance Drug List. (2) Shanghai Xudong Haipu (旭東海普) by TTY Biopharm (台灣東洋): over 100 drug certificates issued by China’s State Food and Drug Administration (SFDA). (3) YSP KuanShan (永信昆山) by YSP (永信): anti-inflammatory drug certificates issued. (4) Sinphar Tian-Li (杏輝天力) by Sinphar (杏輝): 45 Drug Certificates issued, with four in the National Essential Drug List. (5) Beijing UBI (北京優耐特) by UBI (聯亞): HCV&HIV diagnostic testing kits approved for launch. (6) Shanghai Haoyuan (上海浩源) by Medigen Biotechnology (基亞生物): HBV, HCV, and HIV nucleic acid tests approved for launch. (7) UBI Shanghai (申聯藥業) by UBI (聯亞): vaccine for swine foot-mouth disease approved for launch. (8) Shanghai Grape King (上海葡萄王) by Grape King (葡萄王): functional food product manufacturing license obtained.

Abundant manpower and relatively low production costs have prompted Taiwan companies to set up production sites in China. These include: (1) ScinoPharm (KuanShan) (神隆昆山) by
ScinoPharm (台灣神隆): kilo lab and pilot plant for API and process research of scale-up production of key intermediates. **New GMP plant** in Changshou, Jiangsu (江蘇常熟): production of GMP grade drug intermediates started in 2011; API production to be started later. (2) The first phase of a **plant building project of TTY Biopharm (台灣東洋)** in SuZhou Industrial Park (蘇州工業區): oral and injection formulations of anti-cancers; production began in 2012; second phase of plant building project to start in three years. **Shanghai Xudong Haipu (旭東海普)**: products exported to Russia, South-East Asia, Eastern Europe, Africa and South America. (3) **YSP (永信昆山)**: production of formulated drugs, API and chemical intermediates; SFDA GMP certification in 1999, US FDA GMP certification in 2009, Exports to USA started in 2011. **Changshu plant** (under construction): Production of API and intermediates, operation started in 2012. (4) **SCCPC (蘇州中化) manufacturing plant**: Certified facility for GMP with ISO9001 QC and ISO14001 environment management systems; J-GMP certification from PMDA, Japan in 2009; PICS/GMP plant construction started in 2010, to be completed in 2013. (5) **Shanghai Grape King (上海葡萄王)**: HACCP and GMP certified, functional food product manufacturing license obtained. (6) **China Chi Thai Bio (中國濟泰)**: Subsidiary of Chi Sheng Chemical (濟生) in Shanghai; US$ 4 million raised for building manufacturing factory for dialysis fluids, health and skin care products, project started in Q1, 2012, operation to start by the end of the year. (7) **Jiangsu Standard Biotech & Pharm. Co. (江蘇生達生技)**: subsidiary of Standard Chem. & Pharm Co. (生達製藥) in Jiangsu; signed agreement with Japan's largest maker of water-based patches, DIA, for a 44 million RMB joint venture on factory construction for production of water-based patches in China Medical City (中國醫藥城) of TaiZhou, Jiangsu (江蘇泰州).

The main incentives for setting up **R&D Center** in China are three-fold: large talent pool for R&D, large patient pool for clinical trials and mutual interests in developing therapeutics for common diseases. R&D Centers set up by Taiwan companies in China are listed below. (1) By TTY Biopharm (台灣東洋): **TOT R&D Center/Shanghai (東源生物/上海)** - innovative drug development platforms for anticancer and anti-infectious drugs. **TOT Biopharm (東曜藥業)** - oral oncology drug development; therapeutic monoclonal antibody for cancer; production and marketing of special formulation products in 2015. (2) **ScinoPharm /KuanShan (神隆/昆山)**: second R&D center set up by ScinoPharm (台灣神隆) for process R&D of API and intermediates. (3) **SCI PharMtech (旭富)**: API and intermediates process development. (4) **SCCPC (蘇州中化)** by CCPC (中化): GLP standard R&D Center established in 2011; new drug development with 5~8 products to the market per year. (5) Subsidiaries of Yung Shin Pharm (永信): **YSP KuanShan (永信昆山)** - R&D activities. **Farmtec Research (江蘇德芳)** - R&D of API process, formulation, synthesis and manufacture of chemical drugs. (6) **TaiGen Biopharmaceuticals (Beijing) (太景醫藥研發(北京))**: clinical trials and marketing.
Affiliated companies set up in China for market development are cited below. (1) TTY Biopharm (台灣東洋) subsidiaries: Worldco International (榮港生技) - international marketing, alliances with Sunrise Pharm, Univision Pharm, Jiansu Provincial Institute of Materia Medica. Jiang Su BioPharm Tech (江蘇東揚) - marketing and sales. (2) SCCPC (蘇州中化): nationwide distribution channels, marketing teams of over 100 people in Shanghai, Beijing, and Jiangsu, Zhejiang, Canton providences of China. (3) Subsidiaries of Yung Shin Pharm (永信): YSP (KS) (永信昆山) - sales of pharmaceuticals, API, and intermediates. Shanghai Yung Zip Pharm Trading (上海永日) - international trading, API exports to over ten countries including Taiwan, US, Indonesia etc. Globecare Trading (佑康貿易) - supply and sales of food supplements. YSP (HK) (香港永信) - marketing and sales in Hong Kong and Macau.

Other than the formation of affiliated companies, the other business strategy for Taiwan companies in China is R&D Collaboration. Two examples are cited below. (1) Taipei Medical University (台北醫學大學) and Fosun Pharma (上海復星製藥): started in late 2010, development of chemical drugs and biologics to lead in the cross-strait industry and academic collaborations. (2) SinPhar (杏輝) and Modern Research Center for Traditional Chinese Medicine of Peking University (北京大學中醫藥現代研究中心): agreement in 2010 for the former to conduct clinical trials, GAP standard enabling and NDA applications to US FDA, and the latter to conduct preclinical research on botanical drugs, including broomrape (蓯蓉).
5. Taiwan Company as Interface-Partner for Global Pharma in China

In recent years, improvements in cross-strait relationship, coupled with trends in globalization and regional development, have led to increased business and trade cooperation on consumer, high-tech and biotech products between Taiwan and China. Biotech companies of Taiwan have been extending business to China by building factories, setting up branch offices and R&D centers, and forming strategic alliances to access local resources. As a result, many Taiwanese manufacturers have launched new products, obtained certification for new factory, and formed manufacturing partnerships with local companies in China.

Biotech companies in Taiwan have also engaged in joint investment ventures in China to access the local market. For example, Merit Biotech Co. signed a joint venture agreement with Yurun Group Co. in January 2010. A joint venture group was formally set up in 2011 for development, manufacture and sales of immune-enhancing animal products in China. Taiwan’s manufacturers have had to face rising competitions from China, as well as impacts from the relaxation of foreign investment restrictions in China. This has led to a recent wave of business expansion activities in China, including investment in factory construction, layouts of sales channels and formation of R&D collaborations, by Taiwan biotech companies. These activities not only paved the roads to the resource integration for biotech development, but also the presence in global markets for win/win outcomes.

The strengths of Taiwan companies in the cross-strait biotech collaboration can be summed up as: (1) strict adherence to international standards for GLP, GMP, GCP or other regulatory requirements; (2) respect for confidentiality and IP rights; (3) better understanding of Chinese culture and languages, as well as communication skills by management levels with global pharmas; (4) complete infrastructure and value chain for new drug development from the stages of innovative research, preclinical and clinical developments to technology commercialization; (5) growing CRO and CMO industries; (6) ample experience in sales channeling and market expansion in China; (7) experience in partnering with global pharmas. Through alliances with Taiwan companies as interface-partners, especially those with affiliated companies or R&D collaborations in China, global pharmas can more efficiently take advantage of the low costs for drug development and manufacturing in China, while more effectively maintain IP right protections, in the course of market expansion to China. This is also in accord with visions for the cross-strait collaboration: (1) value creation by resource integration for regional biomedical development; (2) enhanced innovative research to fulfill unmet medical needs of Asian countries; (3) quality upgrading to international levels for entry into global markets.