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editorial

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Virtual drug discovery with the rise of Chinese CROs

Drug discovery by an integrated network of external collaborators and/or contract research organizations as a cost-efficient R&D model has been proposed quite some time ago. In fact as early as mid-1990s, companies like Napp have already conducted drug discovery projects from concept to clinical trials by complete outsourcing and working with external partners [1]. The recent suggestion by Morgan Stanley for big companies to exit internal small molecular drug discovery research [2], and the news that large multi-national pharmaceutical companies such as AstraZeneca, GlaxoSmithKline and Pfizer reduced their numbers of employees including substantial numbers of drug discovery scientists promoted renewed interest in virtual drug discovery with fully integrated network of external research partners/collaborators. This review summarizes the pros and cons of various virtual drug discovery models, especially in light of the maturing contract R&D services available in China and multi-national pharmaceutical companies' R&D investment and experiment in this country.

The advantages of conducting drug discovery by a virtual business model are multiple [3]. Firstly, it offers flexibility – companies can access technical skills and scientific expertise on demand, either not present in-house or not cost-efficient to operate. It is less likely to suffer from frequent cycles of 'hire-and-fire' that many companies have been experiencing in the past 15 years that is dependent on the performance of their projects and finance, and the resulting workforce instability. Project management can be highly flexible in adapting to changes in direction or funding. Secondly, it saves money – there are fewer overhead costs, physical facilities to maintain or expensive equipment to depreciate in value. Timelines can be shorter, especially if no massive technology transfer is required, because most equipment and personnel are already in place. Over-booking can occur but has rarely delayed projects in the author's experience of working with Chinese CROs. Thirdly, it fosters entrepreneurship – it reduces the hierarchical organization and facilitates the creation of a dynamic and creative environment, like those present in biotech companies. This is especially beneficial to large pharmaceutical companies. Past experience has taught us that small biotech companies can run multiple projects disproportionate to their size, dealing with complex scientific, regulatory and legal issues with minimum overhead and infrastructural cost. They are more focused on scientific and technical problems, quick in getting to decision points and keen to value creation. Lastly it facilitates the adaptation and integration of the company to its operating environment. This is important for multi-national pharmaceutical companies conducting discovery research in China.

During the past 10 years, there has been a significant rise of CROs in China that have provided services to Western and domestic pharmaceutical and biotech companies covering all aspects of drug discovery research and development. Table 1 lists a few examples of CROs that offer services through their laboratories in China. Those services cover the entire value chain of pharmaceutical R&D and nearly all functional areas. Because of its commodity nature, chemical synthesis was the first service that was outsourced to China by pharmaceutical and biotech companies. Major Chinese CROs such as WuXi Apptech and ChemPartner grew rapidly from a few chemists to thousands of chemists within

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TABLE 1

A selection of China-based CROs (including multi-national CROs that provide services from their Chinese labs/subsidiaries)

Name (HQ/main location)	Service	Note/Web link
WuXi Pharmatech (Shanghai)	Chemistry, *in vitro/in vivo* biology, DMPK, non-GLP tox, formulation, process chemistry and GMP production	The biggest Chinese CRO (>4000 employees) with the 1st certified GMP production/manufacturing in China, currently in the process of being acquired by Charles River Laboratories http://www.wuxiapptec.com.cn/
ChemPartner (Shanghai)	Chemistry, *in vitro/in vivo* biology, DMPK, non-GLP tox, formulation, process chemistry	The 2nd biggest CRO in China (~2000 employees). A multi-ton scale production facility under construction. The firm is preparing for an IPO http://www.chempartner.cn/index.php?id=41
Sundia (Shanghai)	Chemistry, *in vitro/in vivo* biology, DMPK, non-GLP tox, formulation, process chemistry and GMP kilo lab	IP-protected SELO platform for molecular modeling http://www.sundia.com/
Medicilon & Medicilon-MPI (Shanghai)	Chemistry, *in vitro/in vivo* biology, DMPK, formulation, GLP tox/PK	Sister companies: one for pre-clinical discovery services and the other (JV with MPI) for GLP services; government license on working with radio-isotopes http://www.mediciloninc.com/ http://www.medicilon-mpi.com/chinese/services_capabilities.htm
Pharmaron (Beijing)	Chemistry, *in vitro/in vivo* biology, DMPK, formulation, GLP tox PK, process development	Recently acquired Bridge Laboratories China and added GLP services http://www.pharmaron.com/
Chemizon (Beijing)	Chemistry, *in vitro* biology, DMPK, formulation, process development	A division of Optomagic, a Korean public listed company (KOSDAQ:010170) http://www.chemizon.com/
PPD (Beijing)	Chemistry, *in vitro/in vivo* biology, DMPK, formulation, GLP tox PK, process development, clinical trials	Recently acquired Excel PharmaStudies and BioDuro. Provides full range services from pre-clinical discovery, GLP to clinical trials and development http://www.ppdi.com/services/
AsymChem (Tianjing)	Chemistry (synthesis and analytical), formulation, GMP production, API manufacturing	One of the few CROs to provide US cGMP-compliant formulation beyond API raw materials http://www.asymchem.com/en/index.aspx
Omni (Shanghai)	Drug delivery, formulation and stability	One of the few CROs to provide extended release and inhalation formulation services http://www.omni-pharma.com.cn/
Alputon (Shanghai)	Chemistry and compound libraries	A high-throughput parallel synthesis platform acquired from ArQule Inc. (USA) http://www.alputon.com/
Charles River (Shanghai)	Pre-clinical GLP tox and PK	A Chinese division of the well-known multi-national CRO http://www.criver.com/en-US/Pages/home.aspx
HD Bioscience (Shanghai)	*In vitro/in vivo* biology, assay development, high-throughput screening	Specialized in pre-clinical biology. Investors include Lilly and Pfizer ventures http://www.hdbiosciences.com/
CrownBio (Beijing)	*In vitro/in vivo* biology, protein assay development, biomarkers	Specialized in pre-clinical oncology services. Provide human primary tumor xenograft models http://www.crownbio.com/
Frontage (Shanghai)	ADME, bioanalysis and GLP-PK studies	More service, for example clinical studies can be provided through the company's US parent http://www.frontagelab.com.cn/en/index.asp
GenePharma (Shanghai, Suzhou)	Chemistry, siRNA monomers, and oligo design, synthesis	A leading supplier of siRNA in China and one of the rare CROs providing siRNA monomers and oligomers. A kilo lab under construction http://www.genepharma.com/
GenScript (Nanjing)	Bio-reagents, antibodies, molecular biology	One of the few CRO offering biological reagents. Large scale protein production under construction http://www.genscript.com/
TigerMed (Shanghai)	Regulatory affairs, clinical trials	One of the best known Chinese clinical CROs providing Western style clinical development services http://www.tigermed.net/
Rundo-Cronova (Shanghai)	Regulatory affairs, clinical trials	A JV with the Japanese CRO Cronova http://www.rundo-cro.com/En/Menu.aspx?typeid=11

a few years. This has both stimulated the boom of CRO business in China and created fierce competition among the CROs to win projects. Two divergent trends are currently at play for the Chinese CROs to stand out from the competition and ensure future growth. One is to expand the scope of services provided by a single CRO, the so-called one-shop service model. Big CROs like WuXi Apptech and ChemPartner have all hired significant numbers of biologists and specialists of other scientific disciplines in the past few years and can now offer full range of pre-clinical discovery services from chemistry, *in vitro* biology to *in vivo* disease models and production of clinical trial materials. The recent acquisition of Beijing-based pre-clinical discovery CRO BioDuro and clinical CRO Excel PharmaStudies by the multi-national PPD has created a CRO with extended services to cover clinical development in China [4]. Another company following the trend is the Beijing-based Pharmaron that acquired the GLP tox/PK play Bridge Laboratories' China business unit extending its service scope to cover pre-clinical development in addition to existing discovery chemistry and biology services [5].

The other differentiating trend is to focus on a particular specialty of service. Examples of companies following this trend are Crown and HD Bioscience (Table 1). Crown Bioscience, a CRO specializes itself in providing pre-clinical oncology research services, grows rapidly within its 4 years of existence and has recently opened its second research site near Shanghai in addition to its original main site in Beijing. The Shanghai-based HD Bioscience is another specialized CRO offering high-throughput screening and screening assay-centered biology and pharmacology services. Backed by ventures of pharmaceutical companies Pfizer and Eli Lilly, HD Biosciences is consciously focusing on delivering services that are differentiated from many other CROs and add value to its drug discovery customers and shareholders, for example by providing additional leads or chemical starting points to a client's projects.

Virtual drug discovery by cooperating with Chinese CROs has additional potential benefits for those companies that have an ambition to capitalize on the ever enlarging Chinese pharmaceutical market, which is predicted to become the second largest in the world by 2020. Access through the CROs to clinical materials, for example tumor tissue samples, and Chinese key opinion leaders will add value to the on-going projects and tailor them more suited to the Chinese patients' need. Recognizing the value of these novel projects and R&D products to the growing Chinese market, several Chinese CROs are willing to offer the so-called risk-sharing services or flexible FTE rate. Flexible FTE deals require a CRO to adjust FTE headcounts among different service functions while the total FTE numbers remain stable. For example, more FTE headcounts are allocated to biology assay development at the beginning of a new project. Later some headcounts can be shifted to chemistry after biology assay setup is completed. Risk sharing means instead of paying the full FTE rate, customer makes a partial FTE payment or an upfront payment. When the pre-defined project goals are achieved, customer then pays a reward milestone and sometimes a percentage of future revenue stream. In this way, CROs will be compensated significantly more if the project becomes successful by sharing the risks with customers to achieve the project goals. In extreme cases, some Chinese CROs are willing to offer services at material cost to certain projects, usually at pre-clinical GLP study stage, in exchange for the Chinese market rights of the NME under investigation. This does not mean the CRO is interested in pursuing the further development of the NME by itself but rather this gives the CRO the opportunity to sub-license it to a Chinese domestic pharmaceutical company to make a profit that might be bigger than those usually gained from full FTE payment.

Many major multi-national pharmaceutical companies are now conducting drug discovery R&D in China (Table 2), driven by the fast growing Chinese pharmaceutical market, abundant human resource and capital efficiency. Majority of them are doing it in the virtual fashion, especially those that are established more recently. There may be an element of testing water and familiarizing with the country's R&D arena in the preference of the virtual model, but capitalizing on the available CRO services and academic collaborations are certainly the main driver. For example, Eli Lilly, the company that coined the phrase of FIPNet (fully integrated pharmaceutical network) is putting actions where their mouth is. Their pre-clinical drug discovery in China is coordinated by a few executives through a network of academic and CRO collaborations, in addition to their exclusive access to about 200 scientists at ChemExplorer [6]. The advantage of such an arrangement of one main partner supplemented with other external collaborations is that it is much more strategic than a client-service provider one. It saves research cost to Lilly on one hand (roughly 40% cost saving was reported [6]) and avoids the risk of the traditional method of setting up own wet laboratories without deep understanding of its operating environment.

Even for companies that have their own wet laboratories in China, working with Chinese academics and CROs is also an integral part of their drug discovery effort. F Hoffmann-La Roche, for example, has its own R&D laboratories in China and its internal research is complemented by a number of external collaborations with Chinese academics and CROs, covering structural biology, DMPK, disease models, biomarkers and API manufacturing.

The emergence of virtual drug discovery in China has formulated a new customer and CRO relationship. The previous buyer–seller relationship has become more collaborative. Customers treat CROs more like a partner rather than just a service provider. They ask CROs to provide not only a pair of hands, but also brain power. Intellectual contribution to SAR design and key medicinal chemistry issues becomes a must when customers evaluate a CRO for relationship. As a result, Chinese CROs have heavily focused on intellectual capacity buildup by recruiting experienced scientists from overseas.

This new collaborative relationship also demands new management styles and ways of communication from the customer side. Effective managers who have a high level of scientific experience, flexibility, motivation and strong industrial and academic network are key to the success of a virtual drug discovery project. For example, particular attention needs to be paid on potentially unexpected observations/results and ensure they are not lost in communication. Technology transfer can be challenging and time-consuming. Other downside may be the negative impact of a good project manager/coordinator leaving the company is bigger to a virtual drug discovery project than to a conventional all in-house discovery project. Some concerns have also been raised with regard to the likelihood that new experimental and techno-

TABLE 2

A selection of multi-national pharmaceutical companies with R&D activities in China

Name	Year of establishment	Current R&D activities	R&D model/Note
Novo-Nordisk	2002 in Beijing	Pre-clinical and clinical research including protein chemistry, molecular and cell biology through collaborations with local academics and companies, for example strategic partnership with Chinese Academy of Science	Virtual http://www.novonordisk.com.cn/documents/article_page/document/04_english_03_01.asp
Roche	2004 in Shanghai	One of the earliest multi-national pharma companies to establish own pre-clinical R&D (chemistry/biology) labs in China. 1:1 budget distribution between internal and external R&D activities	'brick-and-mortar' plus outsourcing and external collaboration http://www.chinadaily.com.cn/en/doc/2004-01/19/content_300247.htm
Pfizer	2005 in Shanghai (2009 a 2nd site established in Wuhan)	Clinical trials; pre-clinical chemistry/biology, formulation research through a virtual network of local CROs and academics	Virtual http://www.biopharmatoday.com/2009/10/pfizer-rd-in-china-building-a-virtual-rd-network-.html
Eli Lilly	2005 in Shanghai	Pre-clinical discovery research (chemistry/biology) and clinical trials through a network of CROs and academic collaborations, for example strategic partnership with ChemExplorer	Virtual http://www.lilly.com/news/speeches/081119/default.html
sanofi-aventis	2005 in Shanghai (2008 a 2nd center added in Beijing)	Clinical trials and pre-clinical biology research through a network of academic collaborations and CRO services	Virtual http://en.sanofi-aventis.com/binaries/081021_chine_en_tcm28-22382.pdf
Novartis	2006 in Shanghai (2009 a 2nd site for process research and manufacturing in Chengdu)	Becoming the biggest pharmaceutical R&D organization in China with end-to-end pre-clinical discovery to clinical development capabilities	'brick-and-mortar' plus outsourcing and external collaboration http://www.fiercebiotech.com/story/novartis-invests-1b-china-r-d-ops/2009-11-03?cmp-id=OTC-RSS-FB0
Astra-Zeneca	2006 in Shanghai	Clinical trials, pre-clinical translational science, disease knowledge, biomarkers/genetics research	'brick-and-mortar' plus outsourcing and external collaboration http://www.medicalnewstoday.com/articles/44179.php
GlaxoSmithKline	2007 in Shanghai	One of the company's CEDDs (neurodegeneration), conducting end-to-end drug discovery R&D in own laboratories as well as by outsourcing and collaboration	'brick-and-mortar' plus outsourcing and external collaboration http://www.gsk-china.com/english/html/research-development/collaborations-in-china.html
Merck-Serono	2009 in Beijing	Clinical and pre-clinical research on biomarkers, and so on including pharmacogenomics and bioanalytics through a network of collaborations with local academics and companies	Virtual http://www.genengnews.com/news/bnitem.aspx?name=69321270
Bayer-Schering	2009 in Beijing	Clinical and pre-clinical research through collaborations with local academics and companies, for example strategic partnership with Tsinghua University	Virtual http://www.bayerscheringpharma.de/scripts/pages/en/research_and_development/news/rd_center.php
Johnson & Johnson	2009 in Shanghai	Pre-clinical discovery and clinical R&D through 'open innovation', that is working with a broad network of local academics and CROs	Virtual http://www.dddmag.com/news-JJ-Opens-RD-Center-in-Shanghai-061209.aspx

logical experience and competence will be gained in CROs instead of the paying clients.

The Chinese CROs have evolved from the early pure chemistry service providers to integrated drug R&D service partners. Some of them can offer full range integrated R&D services while others specialize in skills and technologies that are complementary to those in pharmaceutical companies. They have built platforms with talents, infrastructures and service experiences during the past several years. Western pharmaceutical and biotech companies have taken advantages of this rise of Chinese CROs and are experimenting new and virtual ways of conducting drug discovery in China. For example, the Cambridge, Mass.-based drug discovery firm Sirtris Pharmaceuticals collaborated with the Chinese CRO Medicilon for the lead optimization of small-molecules that target sirtuins, a family of enzymes associated with the aging process [7]. Sirtris was eventually acquired by GlaxoSmithKline for $720 million, creating substantial value for its shareholders. Recently a California-based biotech company LEAD Therapeutics also benefited from their collaboration with a Chinese CRO ChemPartner. Within 2 years of the collaboration, a clinical candidate was identified that contributed to LEAD's acquisition by BioMarin [8]. There is no doubt that this type of virtual drug discovery will bring more successful examples and have profound impact on the global pharmaceutical R&D, especially in improving capital efficiency and economic value addition of R&D investment.

Disclosure

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