15th SABPA Annual Pacific Forum and 9th SABPA Bio-Partnering

Technical Notes

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Important Disclaimer: Notes were not reviewed by speakers and for reference only

Research and Development in China
Valeria Fantin, PhD, CSO, Zai Lab

China 2017 emerged as 2nd largest in the world with $122.6 billion, $175 billion in a few years.
Increase number of chemical candidates to the global pipeline.
Reasons for such growth: policy, talent, capital, service

2017 CFDA joined ICH as a regulatory member after years of progressive efforts. Chinese government supports regulatory reform.
Significant increase in government and private funding, China in 2017 spends 2.1% GDP in R&D, comparing to 2.7% in US. There is a huge influx of VC.

Zai Lab's HQ was found in Shanghai 2014; last year opens a center in the Bay Area.
Zai Lab's unique business strategy: research, in license and development: develop agents for China prevalent cancer indications and focus on unmet medical needs.
Validate late stage clinical assets, fast to market
Work with partner to develop globally, discover and develop novel drugs through internal research plate form.

Accomplished and execution oriented leadership team
Broad collaboration network with biopharmaceutical companies and academic institutions.
Zai lab oncology portfolio: innovative and synergistic
Strong oncology franchise in 5 common cancers in China with synergistic late stage assets
Also have infectious disease and autoimmune disease pipelines

Discovery pipeline
Zejula best in class PARP inhibitor, launched in Hong Kong, will be in mainland china
2020 vision, leading global innovative biopharma company
2+ products on market, 3+ projects

US & China Combined Development strategy in the Era of IICH

Dan Zhang, MD, MPH, MHM, Co-Founder and CEO of Fountain Medical Development
方恩医药发展有限公司

2015 State council document 44:
Document to the ICH standard even before China joins ICH
Establish green channel, new drug definition, include Chinese sites in global trials

2017 ICH membership:
Initiate FIH trial and get first approval in China
Doc 42: 36 proposals, summary of 2-year effort

2018-19
Unprecedented Gardasil approval in 9 days, 15 direct NDA approvals, Roxadustat first approval
"urgent medical need": 1st batch of 48, 2nd batch of 31, new drug administration law
Improving regulatory environment in China

Pharmacovigilance operation
English to Chinese in 15 days of initial reporting
Impact of ICH on drug development
Speed up the IND process – 60 working days vs 12-24 months, competing for experienced sites

Speed up approval for Import Drug License (IDL): acceptance of foreign data under ICH
Merck HPV vaccine approval in 8 days
48 products invited for NDA in China without clinical data from China

US China development strategy in the era of ICH
Discovery in USA,
Early phase development: US-China combined
Late phase development: majority from China
Regulatory system: US + China

Ethinical difference
Standard of care

Manufacture: MAH, lower cost in China
Commercialization: USA then China
Government insurance vs commercial insurance
Global operation builds up internal clinical operation team
FMD global service, global clients

A Novel Therapy Targeting a Ubiquitous Cancer Survival Mechanism
Qingping Zeng, Founder sand CEO, Fosun Orinove

Fosun Pharma: Business covers all key segments of healthcare industry
Pharma manufacturing and R&D, Distribution and retail, healthcare service, medical device
Efficient operation and steady growth

International capabilities
Joint venture: Fosun pharma and US scientist team, Orinove is the US subsidiary

R&D trend and patient treatment reality:
Latest advances in cancer treatment: targeted therapy, immune checkpoint blockers, cell therapy
Reality: radiotherapy, chemotherapy, significant side effects and poor tolerability

Productive R&D direction:
Make cold tumors responsive to T cells, make chemo less toxic

ER stress in Cancer

Orin1001 profile
Novel IRE1a inhibitor, first in class in early clinical development
FDA granted fast track designation in June 2019
Ori1001 currently in pilot trial in US for solid tumor and BC, NCT03950570
China trial will start early next year for broader solid tumor indications, strong IP opposition for composition of matter and method of use patents
Co-crystal structure published in the literature

Additional oncology targets
ER stress responses in tumor associated Immune cells
Anti-PD-1 + IRE1a inhibitor = synthetic lethal
All cancers under certain degree of ER stress, then UPR, IRE1a, synthetic lethality, leads to apoptosis
IRE1 promotes fibrosis

An exciting opportunity for a novel platform therapy
MYC and IRE1/XBP1 correlation provide rationale for synthetic lethal strategy and next generation oncotherapy
Reduce side effects with standard of care

Programmed Cell Death Pathways and Related Diseases and Aging
Xiaodong Wang, PhD, Director, NIBS Beijing
Co-Founder and Chairman of Scientific Advisory Board, BeiGene

Apoptosis, Caspase mediated Cell Death
Biochemical pathway of apoptosis 1) Extrinsic stimuli to TNFa 2) intrinsic stimuli – mitochondria release cytoC or Smac, which interact with IAP. Smac mimetic - a small molecule neutralizes IAP activities. We will find the right indication of this molecule.

Discovery of an "accidental" cell death
Typical response to TNF+Smac
HT-29 colon cancer cells

Programmed necrotic cell death induced by TSZ
Biochemical Pathway of Necroptosis, small molecule inhibitor developed for RIP1, RIP3, phosphorylated MLKL.

RIP1 inhibitor: >300 compounds, two series <10nM cellular activities, good drug-like profile, efficacious in animal models.

True first in class: do you discover the molecule, or do you discover the biochemical pathway? Knockout RIP3 or MLKL delays mice reproductive system aging, about 80% of the knockouts can get the young mice pregnant, however, none of the new born mice was healthy. These genes control the death of unhealthy sperm cells. Even though the reproductive system is young, the DNA is old.

Detection of phospho-MLKL in the old seminiferous tubules
Induction of necroptosis in testis caused seminal vesicle enlargement, making young mice have “old” testis.

An RIP1 inhibitor retains the fertility rate of wild type mice at an advanced age. animal on control diet, 26% fertility rates, 76% for ones treated with drug.

Partnering for Therapeutic Innovation

Yuan-Hua Ding, Ph.D.
Vice President and Head of Asia Discovery Labs, Emerging Science & Innovation (ES&I), Pfizer Worldwide Research, Development and Medical

Pfizer R&D Focus and Partnering
Delivering breakthrough products
R&D work focus on Prevention, remission, cure
Our therapeutic areas and focus: Rare disease, oncology, inflammation and immunology, internal medicine and vaccines

Pfizer's broad range of partnering vehicles, dedicated funds to enable emerging science, innovative target exploration network, centers for therapeutic innovation, venture investment, strategic alliances and consortiums, emerging science leads

We aspire to be the leader in gene therapy and a partner of choice
Transformational portfolio and capabilities, scalable rAAV manufacturing

>1200 proposals, 90+ projects started, 5 FIH, 15+ patent families, 75+publications
Centers for therapeutic innovation (CTI), great track record of success

Innovative medicine initiative, $2B funds, Asia Discovery labs, dedicated lab facilities in Shanghai, leverage European science communities.
Asia Discovery lab: central lab in Shanghai, emerging science leads at key hubs, Asia innovation fund

Collaborating to unlock and accelerate innovation in APAC: Biotech pharma, access to early and clinical stage assets, and key technology platform. HitGen, DL Med, XtalPi
Academic Innovation Network in the world.

Impact of the Foreign Investment Risk Review Modernization Act: Expanded CFIUS Review of Foreign Investments and New Filing Requirements Impacting Biotech Deals

Justin Huff, JD, of Counsel, Jones Day

Competing policies: The US is open for business and open for foreign investment, and the US will protect its national security interests. US is also putting national security first.

What is CFIUS? An inter-panel agency that review 1) transactions that could result in foreign control of a US business and 2) certain non-controlling investments. CFIUS evaluates whether such covered transactions will threaten the national security of the US.

In 2018, US president signed into law the Foreign Investment Risk Review Modernization Act (FIRRMA) to strengthen and modernize CFIUS.
Bipartisan support in congress as well as from white house and national security policy community
Partial implantation has started under a pilot program
FIRRMA reflects the most significant changes to CFIUS in its history

How FIRRMA changes CFIUS
Expands the scope of CFIUS jurisdiction
Delineates potential exemptions from CFIUS jurisdiction for investments made through funds
Allows short-form “declarations to be submitted in lieu of a formal filing”
Make certain investment subject to mandatory notifications,
Extend the time line for review,
Authorize CFIUS to review certain real estate transactions

Controlling and noncontrolling investments
FIRRMA authorizes CFIUS to review certain non-controlling investments related to critical technology, infrastructure, and sensitive data (TID)

International Traffic in Arms Regulations (ITAR) and EAR
Foreign atomic energy assistance
Nuclear exports and imports
Select agents/toxins
Emerging and foundation technologies (not fully defined)

Technology must be utilized in connection with an identified pilot program industry
Mandatory notifications requirements for accepting resources when an investor receives certain rights such as member, or observer with board seat
Failure to file can result in a fine up to the value of the deal

Critical technology considerations for biotech and life science companies. Mandatory obligation. Critical infrastructure and sensitive data are not mandatory but voluntary at this time. Mandatory filing when foreign government investors have more than 49% interest, and the foreign person invest 25% in US TID business.

Critical technology: Nanobiology, synthetic biology, genomic and genetic engineering and neurotechnology

Critical infrastructure: Transportation, energy, telecommunications, finance, utilities, manufacturing Includes certain companies that supply the military or have received military funding

Sensitive data:
When does the company know too much to make people unconfutable.
Sensitive US government personnel or contractors
Maintain or collect data on over 1M individuals or intent to have over 1M individuals, such as data is an integrated part of the US business primary products or services
Genetic information means information about an individual/s genetic tests, genetic tests of family members of the individuals.

Historically CFIUS only reviews deals with existing business, FIRRMA authorize to review in close proximity to sensitive US government locations, military bases, and at airports and maritime ports.

Most biotechnology companies lack critical technology, pilot program framework may capture more biotech deals, real estate.

Biomedical Innovation System in Chongqing Liangjiang New Area

Yun He, Ph.D.
School of pharmaceutical Science, Chongqing University, Linagjiang New Area Chongqing

Linagjiang New area: First national open area in inland China, June 2010
60% industrial land, 40% residential land

TOP level design, spatial arrangements
Innovation capacity, construction of industrial systems, financial service guarantee

Chongqing University, 50000 students with with 23000 master and PhD students. Recruiter PI 50 people

Panel Discussion: Commercialization and Globalization Strategy for China's Biopharmaceutical Companies

Moderator: Alan Seem, JD, partner, Jones Day
Panelist:
Wen Luo, MD, PHD, CEO/CSO Denovo Biopharma
David Xu, Chief Business Officer, Viva Biotech
Qingping Zeng, Ph.D, Founder and CEO, Fosun Orinnova

Seem: Can you please give a brief introduction and talk about your experience about commercialization and globalization?

Luo: Denovo biopharm acquired late stage assets from big pharm, we focus on first in class and that makes us different from 99% of Chinese companies. I just arrived form Beijing last night with fresh impression from China.

Xu: I am a chemist by training. I worked at Novartis for a long time. I also have complex generic and some biosimilar development experience. Also head of marketing Purdue Pharma. I worked in China for two years. I set up Suzhou Novartis center outside of Shanghai. Current Responsibility is incubation business in Viva Biotech. We are interested in seed round and Series A financing.

Zeng: my background of in R&D and I think from that background about commercialization. It is important to think about your commercialization from the R&D stage.

Seem: Can you give some feedbacks on generally what is going on in biopharma industry in China. A few years ago, foreign companies in china, not much innovation, a lot of Me-too. Has that changed? What is the climate like now?

Luo: Tremendous change has happened. Before it takes 5-7 years to review, now a lot of more aggressive, cutting time down to a few months. Before China mostly has biosimilar, now it is gone. Before generic drugs sell at high price, a lot of globally pharma are driven by generic drugs. Now generic drug price drop by as much as 90%. That drives the whole industry for innovation. Denovo starts with First-in-Class from day one.

Zeng: Fosun's product is generic drug. One China-US difference is patent cliff. Patent expires, drug price drops a lot in US, but that is not the case in China due to the quality control. The situation is changing as the Chinese market is more open towards western pharma.

Xu: I agree with all of these. The bottom line is that for China today favors regulatory reform and the talents are flowing back to china. China also has very mature CRO. Now is the best time and place to start a company in China. Today it is easy to introduce a product in China, too. The market is a quarter of the US size. Branded product will go up. But you still have to play right in China. There are certain things you have to consider before going to china.

Seem: What about pricing? how does that affect global pharma?

Xu: you can't take the US price and go to China. That doesn't go well. Keytruda by Merck is about 50% of the US price. Domestic drug is 50% of Merck's price. China's market is 100% government's money. It is important to get to government's list. A lot of room for improvement.

Luo: When you talk about patent drug, China still has highest price. Many people doesn't realize that china still represent 5% of world market. If you are truly a First-in-Class, you should also go global not only China.

Zeng: China's population is 4x of US. If you cut the price down to 25% you still have the same size. In China, middle class rises quickly, so China market will still be increasing.

Xu: China's market is a bigger pie and growing quickly. The size for innovative medicine is growing faster.

Seem: Orphan drug is getting more acceptance.

Xu: the government is paying more attention to rare disease. But its priority is still at the majority of the population. The current system does not support the pricing as that in US.

Luo: China still doesn't officially have an orphan drug act.

Seem: Commercialization for china. If you have a drug you want to commercialize in China, what is the challenge? Also what is the challenge to take the drug and introduce it around the world?

Xu: in China my impression of the real challenges is that China is one country with many regional differences.

Seem: What is the difference?

Xu: China has coastal, affluence region, but also has the region with lower tier hospital. There is also municipal and provincial difference. There is also a hospital medicine list that you may have to get on.

Zeng: Insurance and provincial governments also have controls. Rural area may only have cheaper drugs.

Luo: It is also true in the US that you may have great drugs but don't know how to sell them.

Xu: Pharma guideline implemented in US in early 2000s prevent you from taking doctors to outings to market the drug, China is in the transition phase. If you have phase 3 trial in China, you have to know which region in China you want to go and consider that in your design. You also have to consider the label by going through the doctors.

Seem: That involves training the doctor, the question is how do you train doctors. I have done IPO in US for Chinese company. You have to talk to the salesperson so that they don't cross the line. That's the US point of view. Chinese has their way. The point is that you are talking to the doctor in the right way. Some companies hire the third party company to do the sales but that doesn't work anymore.

Seem: How do you sell drugs outside of china.

Luo: The key is to align your global strategy in designing your R&D program. By focusing globalization, our candidates all have blockbuster potentials. We only focus on First-in-Class. When we have positive phase 3 we partner with global pharma, they have the experience and resources so we don't have to reinvent the wheel.

Zeng: Chinese companies going outside is still in the early phase. The best strategy is to partner with US company. Fosun is a large pharma in China but we have a small office in US. For our First-in-Class and innovative drug to sell well in the US, partnership is the best approach.

Seem: How do you find good partners? Right partners mean everything. What are the important things you are looking for?

Luo: we have multiple programs. We are in the mid of global phase 3 trials. When you have positive global phase 3, we are focusing for China and US. That package fulfills EMA but not Japan. We have multiple companies in Japan that are interested in us. The bottom line is you have true First-in-Class. If you have a Me-too, there is panic mode because they are behind. So it is good to focus on First-in-Class that have blockbuster potentials.

Xu: To me it all depends on what you are looking for. If you are going to China, you need big company like Fosun and Hengrui. For Chinese company coming to US, similar to Japanese companies coming to US in the 80s. We all want to have First-in-Class. As a commercial person First-in-Class doesn't mean good sale. Addressing the need of the patients you will have a good sell. You don’t want to be 20-in-Class either.

Zeng: Global company coming to China, it is difficult to compete. When Chinese company comes to US, when a US company to help a Chinese company, you can fully realize the potential of the product.