

From Bench to Market: the Successes, Challenges and Opportunities Report on 8th SAPA-WEST Annual Conference

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The eighth SAPA-west annual conference was held on April 19th, 2006 at the Crowne Plaza Hotel in Foster City, California. The all-day event brought together senior executives from biotech/pharmaceutical corporations, entrepreneurs of blooming startups and leading scientists at local biopharmaceutical companies and academic institutions. The theme of the conference was focused on the challenges facing the biotech/pharmaceutical industry and the great opportunities ahead toward globalization. The meeting programs featured plenary speeches that offered the attendants a high-level overview of the challenge and opportunity in our industry. The science-based lectures covering key aspects of the drug discovery and development processes were stimulating and educational to all attendants. As always, the challenges from a business opportunity point of view were vividly analyzed and discussed by business leaders, entrepreneurs and venture capitalists. A significant expansion in this year's program was the presentations from several high profile incubators in China. The Annual Conference, with the great efforts of the organizing committee, the speakers and many SAPA-west members, cumulated a great success.

In his keynote presentation, **Dr. Robert Stein**, President of Roche Biosciences at Palo Alto, gave his view of the pharmaceutical industry, the present and the future. He predicted that pharmaceutical industry would be transformed in significant ways in the next 15 years or so. The pharmaceutical industry, as we know today, with high profitable margin fueled by high prescription price, co-existence of multiple similar drugs made possible by forceful marketing muscle will cease to exist. In the challenging

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environment of healthcare cost pressure and potent competition from low price but efficacious generics, the pharmaceutical industry will have to be innovative to remain vibrant. Runaway cost and declining productivity have been an industry-wide issue. In order for the sector to be competitive and profitable, the industry as a whole will need to take on new approaches to health maintenance and restoration and

to conduct medical research for a better understanding of diseases and diagnoses to develop medicines to treat a subset of patient in order to achieve maximum efficacy. While acknowledging the daunting tasks facing the industry, Dr. Stein offered an encouraging view about the future as well. He was particularly optimistic about Roche's prospect with its leading position in several therapeutic areas and comprehensive medical diagnostic enterprise and its global research networks. Roche has five pharmaceutical research sites globally, including the recently established Roche R&D Center (China) LTD. He pointed out that by working on right projects, applying appropriate resources and organizing the workflow effectively a multi-international organization such as Roche will be able to take on the challenges and be successful.

Mr. Mingde Yu delivered the second keynote speech. He is currently the Executive Chairman of China Worldbest Life Industry Co., Ltd. Mr. Yu gave a broad view on the status of Chinese pharmaceutical industry and the prospect of healthcare system in general. According to Mr. Yu, the pharmaceutical industry in China has been enjoying a rapid and healthy grow over the past decade. Sale of pharmaceuticals manufactured in China has been growing at 18.8% over the five years between 1998-2003 while total net profit increased at an even higher annual rate of 28.8% for the same period. The high rate of growth will continue for some time in the near future. There is a large manufacturing

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capacity in China with over 5000 manufacturers in compliance with GMP regulation. However, it is also well recognized that significant challenges are ahead of the Chinese biotech/pharmaceutical industries, particularly in the areas of low innovation capacity, excessive manufacturing capacity and the lagging rural healthcare system. In the next 15 years, innovation will be a high priority objective in China. A number of key projects have also been identified. Amongst them are the discovery and development of new medicines for the prevention, control of major infectious diseases. Recognizing the issues, policy makers of the central government have outlined several important measures in the recent issued

<<Science and Technology Basic Plans>> to set up the stage for building a healthy healthcare industry. Specific policies are being set and implemented to promote innovation by issuing favorable tax treatment and embracing competition. Many areas that are important to the healthcare industry were given particular priority. The huge healthcare market, the much-improved infrastructure, and the favorable climate created by the policy makers of the central government have made China an attractive place for conducting innovative biomedical research and drug discovery and development.

In these dynamic and evolving environments of the western world and in China, both speakers echoed the key points in how to be successful and thriving in the uncertain future. The other speakers further elaborated those important points.

While focusing his presentation on the critical topic of drug target identification and lead selection, **Dr. Jin-long Chen**, VP of Biology at Amgen San Francisco, first shared with the audiences Amgen's guiding principles in its research and development operation. These guiding principles, instituted by Dr. Roger Perlmutter, Amgen's Executive Vice President of Research and Development, are to focus on grievous diseases, be modality independent, assess efficacy and safety in people, and ensure seamless integration from basic research to commercialization. Some, if not all, of those principles may seem obvious. However, the traditional pharmaceutical industry has spent much effort in engineering modest improvements to existing therapeutics as a means of supporting their established franchise. The traditional approach looks for a disease target that can be approached with a potent and selective molecule that can be manufactured in existing facility. Amgen has been building an interdisciplinary research and development organization

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that addresses the topics at the interfaces between chemistry, biology, molecular biology so as to make cutting edge discovery and to have the ability and capacity to evaluate the best modality for a given target. Choosing a biological target is the anchoring step in a drug discovery process. Chen believed that a good drug target generally should have solid biological relevance to diseases, novelty, druggability and a strategic fit to the organization. He used the orphan G-protein coupled receptor and the orphan nuclear receptor

platforms he helped to establish as examples to elucidate Amgen's approaches toward identifying and selecting the best targets to work on. Genetic manipulation (gene knock in and knockout) enables the ready access to genetically modified animal models. Robust high throughput screening system accelerates the search for endogenous and synthetic ligands for the intended targets. The ready availability of these tools enables the early test of hypothesis and the determination of suitable modality. Central to any early discovery strategy is the ability to screen compound sets against the target of interest. Seamless screening operation ensures rapid and complete exploration of the chemical diversity of company's collection. Lead optimization will then identify and select the potent, safe molecule to allow for expeditiously evaluation of the hypothesis in people with the validated biomarkers to bridge the preclinical and human studies.

Once a lead molecule for modulating the biochemical pathway is identified, the next critical step is to optimize the activity and property of the lead molecule in order to find best molecule with the "developable" properties to advance to clinical evaluation. Optimizing a molecule's pharmacokinetic properties often becomes the focal point of the process. Pharmacokinetics (PK) is a discipline dealing with the study of what would happen to a drug molecule when it is introduced to the body. **Dr. David Lau**, Senior Director at Scios, a Johnson and Johnson Company, covered this important topic in his presentation entitled "Picking the Pearl from Haystack Using Pharmacokinetic Principles". Pharmacokinetics deals with the absorption, distribution, metabolism and excretion of a drug when it is introduced to the body. The study of pharmacokinetics plays at least two important roles in drug discovery: it assists in finding potent compounds that will achieve adequate exposure and thus in vivo efficacy; it also assists in choosing the developable clinical candidate. The study of a compound's pharmacokinetics is intended to find out if the compound has adequate exposure for safety and efficacy testing, sufficient safety margin in preclinical species. The study is also to collect data to allow for accurate prediction of what the human PK might be and what the metabolism profile may look like. It is very important to gain insight about the molecule's potential to interact with other drugs as well as the potential variability. In order to be able to collect sufficient amount of data to allow for a conclusive

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decision, one has to take many factors, including the types of assays and models to use, the timing of sequencing of experiments and the interpretation of data into considerations. A combination of in vitro and in vivo PK and metabolism screening is important for advancement of drug candidates and development. Pharmacokinetic screening does not guarantee success in prediction of human pharmacokinetics. However, when appropriate in vivo and in vitro studies are performed, the odds should be significantly improved. The ability to conduct these experiments, analyze data, and reach to conclusion in a timely and cost effective fashion is utterly important for the success of a drug discovery program.

The sky-rocking cost of developing a new drug has forced the drug companies to invent and implement new ways to conduct preclinical and clinical studies intelligently to increase the likelihood of success. One of the many companies that provide services in these areas is MPI Research. At the SAPA-west annual meeting, Dr. William Harrison, President and Chief Operating Officer of MPI Research, gave a timely presentation entitled “Safety Assessment and Regulatory Affairs”. While touched on a various topics along the process of preclinical and clinical evaluations from both scientific and regulatory perspectives, he emphasized two important areas: the strategy of biomarker study and the concept of DxRx. A broad definition of a biomarker usually refers to any biological measurement that provides actionable information regarding disease progression, pharmacology, safety that can be used as basis for decision making in drug development. A broad definition of a biomarker usually refers to any biological measurement that provides actionable information regarding disease progression, pharmacology, safety that can be used as basis for decision making in drug development. Biomarkers represent tools to improve target identification and target validation, and identify beneficial and adverse drug effects and a way of segmenting patient populations for personalized medicine approaches. Integrating biomarkers across R&D programs improves quality and productivity by improving decision making and gaining greater insight into novel mechanisms in diseases processes, thereby addressing the declining number of new drug approvals. Biomark the new initiatives in industry and the regulatory. Perhaps the most ambitious attempt to find ways to modernize and improve drug R&D is the Critical Path Initiative, a FDA program that released its initial report and recommendations this March. According to the CPI report, the problem with drug R&D isn't that drug companies are failing to come up with good drug candidates. Instead, the problem lies in getting them evaluated in the development stage, where new science has not been adequately applied. Critical Path Initiative is intended to stimulate efforts toward the goals of creating new opportunities to link biomarker development to drug

development and personalized care, through evidence-based medicine.

In 2005, FDA issued a draft Concept Paper on Drug-Diagnostic Co-development. This document provides FDA's

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initial views on co-developing and validating companion diagnostics for use with new (or existing) drugs. Dr. Harrison explained that the concept of combining a therapeutic entity with a corresponding diagnostic test is termed theranostics or Dx/Rx, and he believed that targeted therapeutics is the future of medicine. Other key technologies such molecular imaging, surrogate imaging biomarkers that can be used to diagnose disease and its progression and to quantify drug-target interaction will be employed a lot more extensively in preclinical and clinical settings.

Dr. John Patton, Chief Scientific Officer and co-founder of Nektar, formerly known as Inhale Therapeutics, told the successful story in the development of Exubera®. Exubera® is a fast-acting, powder formulation of human insulin that is inhaled into the lungs via the mouth before meals using a simple-to-use, hand-held device. Nektar developed the inhaler and the powdered insulin formulation for Exubera in partnership with Pfizer. In January 2006, Exubera was approved by the US FDA and the EMEA for the treatment of adult patients with diabetes mellitus. It is the first non-injectable insulin to be approved. Insulin plays a key role in the regulation of glucose metabolism, and defects in either insulin production and/or resistance to its action underlie all types of diabetes mellitus. Type II diabetics has reached to epidemic proportion worldwide. Diabetics is a serious disease, which is the leading causes of blindness, kidney failure among others. While administration of insulin by injection has helped many patients, the inconvenience and fear of injection has created a huge need for an alternative method of delivery. The idea of delivering insulin by pulmonary route was conceived in the 1920s, but remained elusive due to significant technical

The idea of delivering insulin by inhalation was conceived in 1920s, but remained elusive due to significant technical challenges in delivering such a large molecule by this route until the recent technological breakthroughs achieved by Nektar.

challenges in delivering such a large molecule by this route. Patton and fellow co-founder Bob Platz started Inhale Therapeutics in the 1990s and began their quest of developing of an inhaled form of insulin. Major technological breakthroughs were achieved by Inhale in the understanding of the relevance of aerosol dynamics to effective delivery. Factors now known to affect the amount and site of deposition of inhaled, aerosolized insulin include particle size, surface morphology, charge, solubility and hygroscopicity. In addition to developing a suitable insulin formulation for pulmonary delivery, the development of an inhalation device that can be easily and reliably operated by patients is a key technical obstacle that has to be overcome. Exbera, a product resulted from the effort of over 15 years by scientists from many disciplines, is approved in the FDA for the treatment of adult patients with diabetes mellitus for the control of hyperglycemia. In patients with Type I diabetes, it should be used in regimens that include longer-acting insulin. In patients with Type II diabetes, it can be used as monotherapy or in combination with oral agents or longer-acting insulin's. The live demonstration on the operation of an Exubera Inhaler by Dr. Patton attracted the full the attention of audiences. The convenience in use should result in better patient compliance and translate into improvement in glycemia control.

After sharing the difficulties and excitements during the development of Exubera, Dr. Patton offered valuable advise to these entrepreneurs who are ready to pursue their innovative ideas to successful therapeutic products –grab the opportunity and be persistent.

The successful story of Gilead Sciences, headquartered in Foster City, is nothing short of remarkable. At the 8th SAPA-West annual conference, Dr. Gong-Xin He, a director of research at Gilead Sciences, shared the successful experiences in pursuing pro-drug strategy. The company was found largely based on nascent antisense technology platform back in 1987. With the appointment of Dr. John Martin as the CEO, the company reinvented itself and focused its effort largely on antiviral therapeutics including HIV and HBV and CMV, areas there are still significant unmet medical needs. Specifically, Gilead concentrated its effort on developing pro-drugs for the nucleotide-based antiviral agents. The nucleoside and nucleotide analogues exerted their antiviral efficacy primarily by the mechanism of inhibiting viral polymerase or reverse transcriptase activity. Advantages of drugs in this class such as AZT for HIV, Acyclovir for HSV, include low potential of resistance development or slow resistance generation, and long in vivo half-life. However, a major drawback is their lack of oral absorption, presumably due to the highly hydrophilic and ionic nature. Taking Adefovir, an anti HIV and anti-HBV agent, as an example, a pro-drug of Adefovir, called Adefovir dipivoaxil was designed and developed to improve

the oral bioavailability. A once-daily 10-mg tablet formulation (Hepsera™) was approved by FDA in 2002 for the treatment of human hepatitis B. A similar strategy was employed in the development of another pro-drug Tenofovir disoproxil. The

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300-mg tablet, under the trade name of Viread®, has been the workhorse in HIV management treatment since its approval by FDA in 2001. Currently, three nucleotide antiviral drugs that generate a total of 1.5 billion dollar sales annually have made Gilead a sensational successful story.

In addition to the presentations on global environments for the pharmaceutical and biotechnology industry the views of the directions we are heading to and the various important technological challenges we are facing, the conference was enriched with talks on market focus and product latching and marketing strategies.

The participations by several top rated Science/Technology and Business Industrial Parks such Nansa and Suzhou gave the meeting attendants another opportunity to see the much improvement in the infrastructures and the great opportunity for setting up companies and forging business partnerships in China.

“Go East, Young biotech” was the key message of the final presentation of the all-day event, delivered by Dr. Charles Hsu, a venture partner at Pappas Venture, who has invested in several young biotechs with operations both in China and in the US. Hsu's comments reiterated the theme of the 8th SAPA-west conference and summarized the consensus: biotech/pharmaceutical industry will have to be innovative

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