

Globalization of Quantitative Pharmacology: First International Symposium of Quantitative Pharmacology in Drug Development and Regulation

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The First International Symposium on Quantitative Pharmacology in Drug Development and Regulatory Sciences was held this past October in Nanjing, China, marking the first time scientists from around the globe gathered to discuss topics related to quantitative pharmacology in the Far East. With the recent trend toward global drug development and clinical trials in nontraditional countries, China has been regarded by many as the next frontier for the pharmaceutical industry. Quantitative pharmacology embraces all phases of pharmaceutical research and development, providing a mechanism to bridge decision making from one phase of development to the next, and it facilitates

multidisciplinary partnerships through the assembly of both data and models that describe complex biological, biopharmaceutical, and clinical settings. Efforts in China are at an early stage, but it is clear that Chinese scientists embrace the discipline and are keen to promote this methodology in the registration of new drugs in China. While challenges exist, they represent an exciting area of future collaboration.

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Quantitative pharmacology constitutes a multidisciplinary approach that integrates the relationships between disease, drug characteristics, and individual variability (getting the right drug to the right patient at the right dose and time). At its core, quantitative pharmacology provides a quantitative,

data-driven framework that enables rational decision making in preclinical and clinical drug development.^{1,2} Quantitative pharmacology is a cornerstone of the Critical Path Initiative³ promoted by the US Food and Drug Administration and plays a large role in the National Institutes of Health (NIH) Roadmap Initiative.⁴

In a landmark event, the First International Symposium on Quantitative Pharmacology (ISQP) in Drug Development and Regulatory Sciences was held this past October (October 29-31, 2007) in Nanjing, China, marking the first time scientists from around the globe gathered to discuss topics related to quantitative pharmacology in the Far East. With the recent trend toward global drug development and clinical trials in nontraditional countries, China has been regarded by many as the next frontier for the pharmaceutical industry. Through government support, the drug development industry and related infrastructure have been growing rapidly in China, making this an excellent location to host such an important meeting.

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In total, 350 attendees, 49 of whom came from international sites outside China including the United States, Europe, Korea, and Australia, participated in the meeting. Scientists representing academic, regulatory, and industrial communities contributed to the 3-day workshop. Of the 261 registered Chinese participants, 23% were university professors, 36.4% were from hospitals, 27.6% were from pharmaceutical companies, 10.9% were from drug research institutes, and 2% were from the Chinese State Food and Drug Administration (SFDA). The Chinese participants were spread over 140 different sites, covering 25 cities in China. Among them, Beijing (21.5%), Shanghai (10%), Nanjing (18.4%), Guangzhou (6.9%), Hangzhou (5.4%), and Wuhu (6.5%) were the leading metropolitan cities. Other participants were from Hunan, Wuhan, Suzhou, Tianjin, Shijiazhuang, Chengdu, Chongqing, Hefei, and other locations. Among the registered international participants, 25% were from academia, 58% were from pharmaceutical companies, 6% were from regulatory organizations, and 10% were from Contract Research Organization. There were approximately 80 unregistered participants, mainly postgraduate and PhD students from China Pharmaceutical University and other medical universities in Jiangsu province.

The meeting was sponsored by the SFDA, Chinese Society of Quantitative Pharmacology, Chinese Society of Pharmacokinetics, and the *Chinese Journal of Clinical Pharmacology and Therapeutics* and cosponsored by the American Association of Pharmaceutical Scientists, American College of Clinical Pharmacology, Affiliated Yijishan Hospital of Wannan Medical College, Institute of Clinical Pharmacology, Central South University, China Pharmaceutical University, and Jiangsu Drug Research and Development Association. The symposium discussed the latest methodologies in pharmacometrics areas, focusing on pharmacokinetic and pharmacodynamic (PK/PD) modeling and simulation in drug development, regulation, and clinical applications. Professor Rui-yuan Sun, president emeritus of the Chinese Society of Quantitative Pharmacology and editor-in-chief of the *Chinese Journal of Clinical Pharmacology and Therapeutics*, served as the president of the Organizing Committee. Professor Sun provided a review of the past and current research status of quantitative pharmacology in China during the opening ceremony.

The meeting featured a plenary morning session and 2 breakout sessions each day. Symposium topics included drug and biological development and regulation sciences, model-based drug development

(theory and applications), bridging strategies to support global drug development, and clinical policies and guidelines on clinical trials, drug evaluation, and approval. While there were many scientific themes presented throughout, 2 topics were unique and timely given the current issues in global drug development and registration: new approaches to studying Traditional Chinese Medicine (TCM) and the complexity of the global regulatory review and registration process, with emphasis, of course, on the evolving demands on the SFDA. Although these topics have been discussed in other forums, this symposium had the benefit of speakers actively engaged in these areas of research. Four lectures on the SFDA mission, goals, and practices and 7 lectures on various research efforts associated with TCM development were provided. Several other lectures examined the global regulatory comparison of bioequivalence issues, phase I clinical pharmacology trials, first-time-in-man approaches, and ethnic factors in the acceptability of foreign trials. Likewise, both TCM and regulatory sciences were discussed from the standpoint of those engaged in quantitative pharmacology-related roles; the benefit of how quantitative pharmacology research can advance both topics was the central theme of the entire meeting.

The complete program can be found on the meeting Web site (<http://www.qpharmmeeting.com>), and several of the presentation topics and all of the meeting abstracts have been published in the October 2007 issue of the *Chinese Journal of Clinical Pharmacology and Therapeutics* (volume 12, number 10) along with the meeting proceedings. We have summarized the meeting into 3 primary themes, providing highlights for each area.

MEETING HIGHLIGHTS

Traditional Chinese Medicine

Chinese pharmacotherapy has included botanicals for many years, and TCM represents a significant proportion of the medicines prescribed in China. More than 9000 herbal medicines are registered in China, where they are sold in pharmacies as prescription and over-the-counter medicines in special outlets and by licensed practitioners.⁵ Many of these agents are prescribed without the complementary preclinical and clinical experimentation necessary to register these agents in a global regulatory environment. As the World Health Organization supports the incorporation of herbal therapy into mainstream medical care, a more

global investment in the science of TCM seems justified. This meeting provided an opportunity to examine how best to characterize some of these complex drug products while leveraging the long-standing clinical experience with these agents. Dr Jin-hui Dou gave a lecture titled “Developing Plant Derived Mixtures as Botanical New Drugs in the US,” providing an FDA reviewer’s perspective on the pros and cons of developing new drugs from botanical mixtures. He listed the following as essential approaches to addressing the consistency issue in botanical drug development: stringent botanical raw material and process controls, fingerprinting and quantitative analysis of botanical substances, bioassays, and multiple-batch clinical studies. While the first botanical new drug application was approved in 2006 (green tea extract as a topical drug for genital warts), all indications suggest that, despite some concerns, TCM will continue to represent an expanded area of regulatory review for the United States.

Several presentations addressed the strides being made to close the gap in information regarding TCM. Dr Shufeng Zhou gave a lecture titled “Metabolism and Transport of Drugs and Chinese Herbal Medicines: From Molecule to Malady,” illustrating the necessity of conducting absorption, distribution, metabolism, and excretion studies in the quest to establish the safety and efficacy of Chinese herbal medicines. Dr Chang-Xiao Liu gave a presentation titled “Challenges in Research and Development of Traditional Chinese Medicines,” in which he described the basic process of studying plants used in TCM as well as the challenges in the discovery and development of new agents, including a discussion on the safety of existing products such as Ginkgo. Dr Xiao-Dong Liu, in his presentation titled “Questions on the Pharmacokinetics of TCM,” explained some of the unique challenges in describing the pharmacokinetics of these multicomponent drug products and provided examples of PK analysis of berberine and palmatine following oral administration of Huanglian-jie-du-tang (Goldenseal), originally created by Dr Wang Tao in 752 AD, which is claimed to strengthen the immune system. The challenge, as for small molecules, is to develop methods to explain the bioactivity of associated compounds. The additional hurdle with TCM is that multicomponent strategies often elicit off-target effects.⁶ Efforts to develop a pharmacologic index to reflect the overall effect of TCM are theorized to be the next necessary step in this endeavor and will require complementary PK strategies as well.

Additional presentations by Dr Ning-ning Xiong titled “Scientific Issues on the Clinical Evaluation of Chinese Traditional Medicine” and Dr Bin-Xiang Yuan titled “Cell Membrane Chromatography—Drug Discovery From Herb Complex Systems” highlight the diversity of the research presented on the topic of TCM. As the gap in knowledge in basic science is closed with these products, it is hoped to be only a matter of time before biomarker and pharmacogenetic strategies are incorporated into the preclinical and clinical characterization of these medicines.⁷ It is clear that they represent both an economically attractive market and a new source of potentially vital, albeit complicated, strategies to treat a variety of health complications.⁸ It also seems evident that the concept of personalized medicine has been long practiced with TCM, and the Chinese physician-patient relationship is largely constructed from implicit belief in such an approach.

Regulatory Review: Global Differences in Approach, Process, and Decision Making

Efforts to harmonize the process and the guidance provided by the global regulatory community have achieved a level of standardization that has improved the registration of new molecular entities from the standpoint of both consistency in the submissions and the nature and timing of the review. The International Council on Harmonization (ICH; <http://www.ich.org/cache/compo/276-254-1.html>) has provided a mechanism to facilitate such efforts for the United States, Europe, and Japan. China’s regulatory history is much shorter and somewhat encumbered by historical practices. While the US FDA recently celebrated its 75th anniversary, its counterpart in China, the SFDA, has existed for less than 25 years. Great progress has been made in China via the creation of a codified system similar to that used in nations supporting international harmonization (<http://eng.sfda.gov.cn/cmsweb/webportal/W45649037/A48335975.html>), although significant issues remain. One of the more pressing concerns in China is the staffing relative to the demand for regulatory review. In 2005, the Center for Drug Evaluation in China had only 120 employees and approved 1113 drug applications. Over the same period, the US FDA, with a staff of 1800, approved 20 new drugs. Recently, the SFDA pledged to spend \$1.2 billion to upgrade drug and food oversight and is working to cut the review time to approve the sale of priority drugs in China.⁹ Dr Zi-li Li described such differences in detail in a presentation titled

“Chinese SFDA vs. US FDA—Understanding Chinese Regulatory Agency and Role of China in Global Drug Development.” He discussed the necessary improvements in late-phase drug development capacity that need to occur at the SFDA with respect to clinical trial oversight and the design of clinical trial protocols, as well as improved interaction with US and other regulatory agencies. Dr Ke-jian Zhang provided a lecture titled “Status of New Drug (Chemical Drugs) Application and Review in China,” giving a review of the current SFDA infrastructure and organization as well as the current review process. Dr Mei-ling Chen of the US FDA presented “A Contemporary View of Bioequivalence and Therapeutic Equivalence.”

The biggest discord between the current SFDA practices and the concerns of global innovator companies has to do with the definition of what constitutes a “new chemical entity” and the assurance that the confidentiality of data submitted for drug registration will be maintained along with the linking of drug approvals to patent protection.¹⁰ Another concern is the lengthy time required for clinical trial approval in China, which precludes participation in many global trials. This was discussed in a roundtable discussion with representatives from the SFDA, China Pharmaceutical University, international companies, and local drug companies. While regulatory approval can be made between 2 weeks and 3 months for many Western countries, it often takes 9 to 12 months in China. Although no agreement was made on ways to improve the Chinese clinical trial approval process, it was acknowledged that further discussion in a more formal forum is greatly needed.

Most of the didactic presentations were in areas related to worldwide registration and the strategies used in ICH countries. Specifically, Dr Niranjan Rao gave a presentation titled “Ethnic Factors in the Acceptability of Foreign Clinical Data: The Role of ICH E5 Guidance in International Drug Development.” Dr Ren-li Teng gave a lecture titled “Points-to-Consider: Bioequivalence Studies vs. Biowaivers,” and Dr Kenneth Kim presented “Integrating Asia Into Global Development Thru Bridging Trials.” There were also presentations comparing and contrasting approaches in the United States and China. Dr Jian-feng Lu presented “Comparison of Clinical Pharmacology Between China and US,” while Dr Pei Hu discussed phase I studies in China. Dr Hu also gave a review of the history and evolution of good clinical practices in China highlighting the regulatory oversight and illustrating the process with examples from her unit at PUMC. In addition, Dr Hequn Yin presented

“Innovative First-in-Man Clinical Trial Approaches: Microdosing, eINDs and Real-Life Applications,” and Dr Steven Zhang presented “Application of Population PK/PD in Clinical Development and Global Regulatory Submissions,” both of which highlighted the innovation in clinical development sought by the global regulatory community and supported by the FDA’s critical path initiative.

Applications of Quantitative Pharmacology

In its landmark Critical Path Initiative, the FDA called for drug sponsors to invest more heavily in drug development sciences, particularly in the area of clinical pharmacology and pharmacometrics. Their expectation is that more informative trials conducted with the intention of more explicitly identifying the therapeutic window will yield better medicines with less consumer risk and a more rigorous understanding of drug management at the individual patient level.³ Implicit in these comments was a plea for more rigorous adoption of quantitative pharmacology. This is similar to the NIH Roadmap Initiative, which recognizes the need to advance our understanding of complex biological systems by focusing research on quantitative understanding of the interconnected networks of molecules that comprise cells and tissues, their interactions, and their regulation.⁴ The ISQP meeting featured several academic, industrial, and regulatory applications of quantitative pharmacology from Chinese and Western perspectives. Dr Thaddeus Grasela gave a keynote presentation at the first plenary session titled “Delivering on the Promise of Pharmacometrics,” which included many historical examples of quantitative pharmacology applications primarily focused on late-stage drug development. Dr Xiao-hui Huang provided a complementary view titled “Status of PK/PD Modeling Research in China.” Other areas of interest and application included response surface modeling (Dr Wei Lu), model-based approaches to drug-drug interactions (Dr Min Zhu), and mixed-effect modeling of drug-related QT effects (Dr Charles Oo).

In addition to Dr Grasela’s talk, several other presentations highlighted with examples the value of quantitative pharmacology application to various drug development phases. Dr Andrew Chow presented “PK/PD Modeling—A Defined Role & Responsibility in Global Pharmaceutical Research & Drug Development,” and Dr David D’Argenio presented “PK/PD Modeling at the Preclinical/Clinical Interface.” The impact of modeling and simulation on regulatory submissions and decision making was demonstrated by

Dr Raymond Miller, who discussed “The Strategic Role and Application of PK/PD Modeling and Simulation in Drug Development,” and Dr Jaap W. Mandema, who presented “Value of Model-Based Meta-analyses for Drug Development and Approval.” Dr Jun Shi presented “Model-Based Strategy for Antibiotic Development Decision Making.” An academic perspective was provided by Dr Jeff Barrett whose discussion was titled “Integrating Modeling and Simulation Strategies Into Targeted Translational Research,” and he led a roundtable discussion titled “Curriculum Development for the Next Generation Pharmacometrics Scientist.” It was very clear from the roundtable discussion that scientists recognize that the problem and (it is hoped) the solution to the deficit of trained pharmacometrics scientists are global.

Another facet of the Critical Path Initiative is the need to employ more novel study designs in drug development, particularly at the dose-finding stage of human testing. To this end, the ISQP conference featured 3 lectures exploring this theme. Dr Michael Fossler presented “Theology of the Non-conformist—An Argument for the Use of Bayesian Statistics in Phase 2,” Dr Michael Brown presented “Adaptive Dose Finding Using Group Sequential Design,” and Dr Xin Huang presented “Adaptive Designs: A Industrial Perspective.” Each presentation provided very compelling case studies for these approaches. Although adoption of Bayesian methodologies may not be as fast as some may hope, it is clear that the climate for change with respect to novel study designs is favorable.

Finally, an interesting bedside application of quantitative pharmacology was presented by Dr Haitang Xie and colleagues. In areas of the world where infusion pumps are prohibitively expensive, it is difficult to safely and quickly administer loading and maintenance doses of cardiac drugs to patients in the hospital. Dr Xie presented an extension of the double-bottle infusion method originally developed by Professor Rui-yuan Sun to the case of a drug whose disposition corresponds to the 3-compartment model. This multibottle infusion technique was shown to be effective in rapidly and safely reaching target propofol concentrations in experimental animals and is a nice example of the usefulness of quantitative pharmacology at the bedside.

CONCLUSIONS

Although pharmaceutical research and development have been pursued on a global scale for many years, it is only recently that these efforts have been extended

to all countries of the world. Thomas L. Friedman’s bestselling book, *The World Is Flat: A Brief History of the Twenty-first Century*, describes the lowering of trade and political barriers coincident with exponential technical advances of the digital revolution. As it is now possible to do business instantaneously with billions of other people across the planet, the evolution of a truly worldwide research collaborative seems likely. Friedman’s Globalization 3.0 is driven by individual freelancers and innovative startups all over the world (especially in India and China), not just by major corporations or giant trade organizations. Hence, all sectors of the pharmaceutical research community are equally exposed to this phenomenon and will likely participate in the globalization of pharmaceutical research and development in both common and unique ways.

Quantitative pharmacology embraces all phases of pharmaceutical research and development, providing a mechanism to bridge decision making from one phase of development to the next. It also allows the creation of multidisciplinary partnerships through the assembly of both data and models that describe complex biological, biopharmaceutic, and clinical settings.¹¹ Likewise, clinical pharmacology sits at the focal point of much of this effort and often represents an area where decisions about a drug product’s ultimate viability are addressed. While this approach has been discussed previously, it is only recently that examples of the end-to-end approach have been discussed or described. Although such efforts in China are at an early stage, it is clear that Chinese scientists embrace the discipline and application and are keen to promote this methodology in the registration of new drugs in China. While challenges exist, particularly in the adaptation of these methodologies to TCM, they are not unsolvable and represent an exciting area of future collaboration.

Expectations should be high for the continuation of efforts to globalize the application of quantitative pharmacology in various settings in which the research and development of xenobiotics is explored. The extension of these efforts not only unites talented scientists worldwide but also expands the research and development space promoting new ways of looking at old problems.

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