



SAPA-GP Workshop: Non-Clinical Drug Safety Evaluation
 Pinecrest Country Club - Lansdale, PA
 Saturday, December 12, 2009



The obstacles to successful drug development are numerous and well appreciated. Despite huge outlays by the worldwide pharmaceutical research enterprise, the number of new chemical entities brought to market has actually declined in recent years, even as the cost of developing them has increased significantly. Safety is one of the two main factors contributing to the low success rate from preclinical development to first-in-man studies, and eventually to marketing authorization.

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PROGRAM

8:30-9:00	Registration
Morning Session	
Moderator: Yun Zhang (YZ), Ph.D., DABT	
9:00-9:05	Tsang-Bin Tzeng, President; SAPA-GP at AZ Welcome and Introduction
9:05-9:10	Yun Zhang (YZ), Merck Opening and Program Overview
9:10-9:50	John Erve, Pfizer Role of Metabolism in Drug Toxicity
9:50-10:30	Weiping Shao, Merck Investigative Toxicology and Biomarker to support lead optimization
10:30-10:45	Coffee Break & Networking
10:45-11:30	Li Li, Novartis General Toxicology and eIND/IND and NDA
11:30-12:00	Haisong Ju, Novartis Safety Pharmacology and Cardiovascular Safety Evaluation
12:00-12:30	Chunhua Qin, Merck Genetic Toxicity Testing: Principle, Regulatory Requirement, and Risk Management
12:30-1:30	Lunch and Networking
Afternoon Session	
Moderator: John (Zhihua) Zhang, MD, PhD	
1:30-2:20	Robert Parker, Huntingdon Life Sciences Preclinical Studies for Assessing Developmental and Reproductive Toxicity (DART)
2:20-2:50	Yi Jin, Novartis Carcinogenicity Assessment During Drug Development
2:50-3:20	John Zhang, EnzymeRx Non-Clinical Drug Safety Evaluation of Biologic Drugs
3:20-3:35	Coffee Break & Networking
3:35-4:15	Kewen Jin, Charles River Lab, Shanghai Perspectives on Chinese toxicology CROs from the Vendor's Standpoint
4:15-5:00	Ernest Bush, Cambridge Healthtech Associates (CHA) Considering GLP CROs in China: Top 5 Questions Asked

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SAPA-GP Workshop: Non-Clinical Drug Safety Evaluation

The obstacles to successful drug development are numerous and well appreciated. Despite huge outlays by the worldwide pharmaceutical research enterprise, the number of new chemical entities brought to market has actually declined in recent years, even as the cost of developing them has increased significantly. Safety is one of the two main factors contributing to the low success rate from preclinical development to first-in-man studies, and eventually to marketing authorization. This workshop is designed to provide insights into optimal non-clinical safety programs with emphasis on the following points:

- This program will include the fields of DMPK, DART, safety pharmacology, and toxicology. The DMPK presentation is to provide participants an appreciation of the role metabolism plays in the drug safety evaluation.
- The ICH M3 R2 guidance continues to drive the non-clinical safety program. A strategic/predictive non-clinical safety program describing the purpose, scope, and timing of a series of non-clinical studies should support the clinical plan and marketing approval of new products. As such, the non-clinical safety development program is designed to support the safe clinical use of biopharmaceuticals.
- Recently, the pharmaceutical industry looks to China and other emerging markets for both their cost effectiveness in R & D and rapid growth of their product sales. Contract research organizations (CROs) in drug discovery and early development in China are in their exponential growth phase. This conference also provides an inside and outside view of the status, opportunities, and challenges of Chinese GLP toxicology labs.
- Presentations will be given by experienced industry scientists/leaders to address the science, processes, and regulatory expectations for successful drug developed.
- The attendee will learn key concepts in the considerations for designing a non-clinical safety development program for a biopharmaceutical product to advance a compound or “kill” a compound efficiently.

Please bring this program description to the attention of your friends, colleagues and business associates. We look forward to welcoming you to the member conference / workshop on non-clinical drug safety evaluation.

Date: Dec. 12, 2009

Time: 9:00 AM – 5:00 PM

Location: PineCrest Country Club

Operation Organizer:

101 Country Club Drive

Ronnye Schreiber

Lansdale, PA 19446

President, PlanetConnect, Inc.

Program Co-Chairs: Yun Zhang (YZ) and John (Zhihua) Zhang

SAPA GP key EC members: Tzeng Tsang-Bin (President 09-10), Jingsong Wang (President 10-11), Yan Li (President 08-09), Zhongda Zhang (Treasurer and the former President), Jiang Tao (Business Director)

Agenda

8:30-9:00 Registration

Morning Session Moderator: Yun Zhang (YZ), PhD, DABT

9:00-9:05: Welcome and Introduction
Tsang-Bin Tzeng, PhD
President, SAPA-GP
Sr. Director, Clinical Pharmacology/DMPK, AstraZeneca

9:05-9:10: Opening and Program Overview
Yun Zhang (YZ), PhD, DABT
Research Fellow, General Toxicology, Safety Assessment, Merck

9:10-9:50 Role of Metabolism in Drug Toxicity
John Erve, PhD, DABT
Principal Research Scientist II, Pharmacokinetics Dynamics and Metabolism, Pfizer

Reactive metabolites are a concern due to their potential role in drug toxicity. Despite our understanding of bioactivation pathways and ability to minimize reactive metabolite formation, toxicity remains a cause of failure during drug development. This talk will cover some general principals of drug metabolism as relates to drug toxicity and review some structure-toxicity relationships that have been identified.

9:50-10:30 Investigative Toxicology and Biomarkers to Support Safety Lead Optimization
Weiping Shao, PhD
Research Fellow, Laboratory Sciences and Investigative Toxicology (LSIT), Safety Assessment, Merck

For several years, the pharmaceutical industry has been suffering from a lack of productivity in terms of the number of new chemical entities approved. Multiple factors have contributed to this trend. Toxicity is the single most significant constant of attrition to drug development pipelines. This alone warrants investments in strategies and technologies and the necessity of moving safety assessments to the discovery and early preclinical stages of drug development. This presentation illustrates the strategies and major techniques currently in use for predictive safety testing from the discovery to the advanced preclinical stage.

10:30-10:45 *Coffee Break & Networking*

10:45-11:30 General Toxicology, eIND/IND, and NDA
Li Li, PhD, DABT
Principal Fellow, Project Safety Assessment, Preclinical Safety, Novartis

General toxicology is part of the multi disciplined science called preclinical safety, which includes safety pharmacology, genetic toxicology, general toxicology, reproductive toxicology, neonatal/juvenile toxicology, carcinogenicity, immunotoxicology, photo-

safety, investigational/mechanistic toxicology, etc. The purpose of conducting toxicology studies is to identify potential safety hazard (target organ toxicity) of new drug candidates, establish dose-response for target organ toxicity, assess potential safety risk for human in clinical trials, set the initial dose for first in human trials (eIND/IND), and ultimately support new drug registration (NDA). Although the toxicology program for a new drug candidate is driven by current regulatory environment, it should be also tailored for the clinical program (treatment duration and indications), and the characteristic of the compound itself. The optimized toxicology program based on regulatory needs and scientific justifications is necessary to effectively support drug development and successful registration of a new drug.

11:30-12:00 Safety Pharmacology and Cardiovascular Safety Evaluation

Haisong Ju, MD, PhD

Associate Director, Head of Safety Pharmacology-US, Preclinical Safety, Novartis

Safety pharmacology is a distinct scientific discipline that integrates the best practices of pharmacology, physiology, and toxicology. Safety pharmacology studies are required by international regulatory guidelines (ICH S7A/S7B) to assess the impact of a new chemical entity or biotechnology-derived product on the function of vital organ systems (cardiovascular, central nervous, and respiratory) before first-in-man clinical trial. Safety pharmacology studies constitute an important component of the initial safety evaluation, and are reviewed prior to the first administration to human studies. Hazard identification and risk evaluation are key aspects of the evaluation. Safety pharmacology plays a critical role in the pharmaceutical industry, by providing valuable insight into potential adverse effects of drug candidates. These data can be critical in design of clinical trials and are used to guide physicians in the safe conduct of clinical trials. Safety pharmacology offers a variety of large and small animal models, using state-of-the-art technologies, to complete the safety pharmacology core battery of studies. Supplementary or follow-up studies are offered using tailored solutions for comprehensive investigations. The current presentation will be focused on safety pharmacological assessment of cardiovascular system with emphasis on QT prolongation and associated risk.

12:00-12:30 Genetic Toxicity Testing: Principle, Regulatory Requirement, and Risk Management

Chunhua Qin, MD, PhD

Sr. Research Genetic Toxicologist, Genetic Toxicology and Molecular Carcinogenesis, LSIT, Safety Assessment, Merck

Genetic toxicity testing is an important component of drug safety evaluation. The scope of the tests and the standard testing battery for pharmaceuticals are defined in the ICH Guidelines (S2A: "Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals", 1995; and S2B: "Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals", 1997). This presentation will introduce the principles of genetic toxicity testing, regulatory requirement, testing timeline, data interpretation, follow-up studies (and methods), and risk management of pharmaceuticals with genotoxicity potentials. The regulatory requirement on the qualification and control of potential genotoxic impurities will also be discussed.

12:30-1:30 *Lunch and Networking*

Afternoon Session Moderator: John (Zhihua) Zhang, MD, PhD

1:30-2:20 Preclinical Studies for Assessing Developmental and Reproductive Toxicity (DART)
Robert Parker, PhD, DABT
Director of DART Division at Huntingdon Life Sciences' Princeton Research Center, NJ

The objective of this presentation is to provide the methodologies used during the performance of reproductive and developmental preclinical safety toxicity testing for evaluation of pharmaceuticals (with emphasis on biotherapeutics), compliant with the latest international guidelines. Prior to the ICH, multiple agencies and countries promulgated their own testing guidelines resulting in time-consuming and overlapping testing and data sets, high use of animal resources, and high testing costs for world-wide registration. While the United States, the European Community, and Japan have worked together to harmonize their test guidelines via the ICH, there still remain differences on the design and timing of these studies in relation to the clinical trials. These differences will also be highlighted in this presentation.

2:20-2:50 Carcinogenicity Assessment During Drug Development
Yi Jin, PhD, DABT
Sr. Project Team Member (PTM), Preclinical Safety, Novartis

Carcinogenicity assessment is the important part of drug safety evaluation and represents the most expensive and the longest duration of the toxicology studies during drug development. Results of carcinogenicity studies will have impact on development of drug candidates and potential of marketing. Conducting a carcinogenicity study has been highly regulated by health authorities with various requirement. This topic will cover current regulatory requirement for carcinogenicity assessment, carcinogenicity study types and study design, and carcinogenicity study protocol submission.

2:50-3:20 Non-Clinical Drug Safety Evaluation of Biologic Drugs
John (Zhihua) Zhang, MD, PhD
VP, Preclinical R & D, EnzymeRx LLC, NJ

Biologic drugs are a very diverse class of drugs, and yet have very common characteristics. This class of drugs gets a lot of attention due to their high profit margin and basically no generic competitions. It is estimated that approximate 50% of the drugs in research and development by 2015 will be biologics or related drugs. Pharmacologically, biologic drugs are usually very specific to their targets and the common toxicities of biologic drugs usually are its exaggerated pharmacological effects. Therefore, selection of a clinically relevant species in safety evaluation is very critical. In addition, immunogenicity is a potential issue for this class of drugs. This presentation will focus on species selection and immunogenicity in drug safety evaluations.

3:20-3:35 *Coffee Break & Networking*

3:35-4:15 Perspectives on Chinese toxicology CROs from the Vendor's Standpoint
Kewen Jin, MD

General Manager of Charles River Laboratories (CRL) China Preclinical Service Company, Shanghai

The presentation will discuss the fast evolving preclinical CRO landscape in China, the prospect for future growth, and the key issues and challenges.

4:15-5:00 **Considering GLP CROs in China: Top 5 Questions Asked**

Ernest Bush, PhD

Managing Director, China Preclinical Management Services (CPMS)
VP & Scientific Director, Cambridge Healthtech Associates (CHA)

CHA and its subsidiary have been evaluating, educating and utilizing GLP CROs in China since early 2006. Initially they conducted several collaborative projects to identify and qualify the top CROs. Then in 2007 they formed China Preclinical Management Services to assist Western companies in leveraging opportunities for conducting studies in China as well as help Chinese companies conduct studies that will meet Western regulatory standards. This talk will summarize the major issues, concerns and benefits of working with GLP CROs in China.

5:00 **Conference Adjourn**