NorCal Society of Toxicology Spring Meeting

Drug development: from small molecules to biologics

Date: Thursday, May 6th, 2010

Location: SRI International
333 Ravenswood Avenue
Menlo Park, CA 94025

Click here to register http://www.acteva.com/booking.cfm?bevaid=202101

Program

Morning

8:30 Registration and continental breakfast

9:20 Welcome

9:30 Case Files of the FDA – How Not to Develop a Cancer Drug
William David McGuinn, Jr., MS, Ph D, DABT, Division of Drug Oncology Products, CDER, FDA

10:15 Nonclinical Evaluation of Oral Antiviral Agents
Grushenka H. I. Wolfgang, Ph.D, DABT, Vice President, Drug Safety Evaluation, Gilead Sciences, Inc.

11:00 Toxicological Considerations for Oligonucelotide Therapeutics
Page Bouchard, DVM, DACVP, Global Head of Preclinical Safety, Novartis

11:45 Lunch (Optional: Lunch with an Expert program)

Afternoon

1:00 FDA and Nanotechnology for Medical Products
Richard A. Canady, PhD, DABT, Senior Advisor, McKenna Long & Aldridge, LLP

1:45 Assessment of Genotoxic Impurities in Small Molecule Drug Candidates
Kurt Black, PhD, DABT, Comparative Biology Safety Science, Amgen.

2:30 Break

2:45 Safety Evaluation of Antibody Drug Conjugates
Kirsten Achilles-Poon, BS, Safety Assessment, Genentech

3:30 Incorporation of Fertility Endpoints in Non-human Primate Chronic Toxicology Studies for Monoclonal Antibodies
Anu Vaidyanathan, Ph.D., DABT, Safety Assessment, Genentech

4:15 Wine and cheese reception and poster viewing

Registration

Registration is $25 for NorCal SOT members, $35 for nonmembers and FREE for students/post-docs. Students are encouraged to bring posters documenting their research and will receive $50 for doing so. Students may have their posters printed by contacting Steve Dizio at sdizio@dtsc.ca.gov. All attendees will have the opportunity to participate in a Lunch with an Expert program.

Register online at http://www.acteva.com/booking.cfm?bevaid=202101

Sponsors

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Presentation abstracts and speaker biographical sketches

Case Files of the FDA – How Not to Develop a Cancer Drug

William David McGuinn, Jr., MS, Ph D, DABT, Division of Drug Oncology Products, CDER, FDA

The promulgation of the new ICH S9 document on the development of new cancer drugs has brought some changes in regulatory requirements. It has also caused some confusion about what studies are needed and when they should be submitted in support of clinical studies. S9 was designed to describe the development of new drugs for patients with life threatening disease, but it does not cover all situations were drugs designed to treat or prevent cancer. This is particularly true with diseases that may be potentially cured by surgery and the drugs are given as adjuvant treatment to decrease the incidence of recurrence or where a drug will be given to health normal volunteers. Thus, there is a sliding scale between the minimal requirements of S9 and the much more stringent requirements of ICH M3, the document that describes the development of drugs for non-life threatening conditions. In this talk, I will discuss various situations based on real examples (of course without identifying the drug) where the minimal requirements of S9 may not be adequate. I will give examples where development has been to sparse requiring regulatory action and examples where a sponsor conducted unnecessary studies. I will also discuss the process of writing a drug product label and the studies necessary to support that product label.

David McGuinn Jr., MS, Ph D, DABT,
Dr. McGuinn is originally from Asheville North Carolina. He has a bachelor's degree in Physics and a Masters degree in Inorganic Chemistry from North Carolina State University. In 1988, he received a Ph. D. in Biochemical Toxicology from North Carolina State University for work done on the kinetics of ligand binding at the active site of Cytochrome P450 in the lab of Professor Ernest Hodgson. From 1988 to 1993 he was an NIH Fellow and lecturer in toxicology and pharmacology at the Medical school of Texas A&M University developing biological therapies for cyanide and war gas exposure in the lab of Professor James Way. Since 1993 he has worked for the Division of Drug Oncology Products at FDA as a primary toxicology reviewer. He is one of the guys you send the non-clinical studies to and yes someone does actually review all that stuff. In addition to his research, he has published numerous papers on drug development and the approval and toxicity of new cancer drugs. He is a Diplomate of the American Board of Toxicology and a certified rescue scuba diver in case anyone starts to drown during this presentation.

Nonclinical Evaluation of Oral Antiviral Agents

Grushenka H. I. Wolfgang, Ph.D, DABT, Vice President, Drug Safety Evaluation, Gilead Sciences, Inc.

Viral infections can be acute (e.g. influenza), chronic yet curable (e.g. Hepatitis C (HCV)), or chronic and only manageable by long-term viral suppression (e.g. HIV or Hepatitis B (HBV)). When designing nonclinical programs for oral antiviral agents, one

needs to consider the type/duration of infection, patient population, and the ability of the virus to mutate which necessitates the use of drug combinations to control the virus. This presentation will review nonclinical support needed for the development of HIV and HCV antiviral therapeutics. The development path for HIV agents is well established as there are more than 20 approved agents. While the field of HIV treatment has progressed rapidly there are still improvements to be made to ensure patients have regimens available with long-term efficacy and safety. For HCV, the standard of care (SOC) treatment consists of ribavirin and pegylated interferon; this regimen is not well tolerated and is only ~50% efficacious in some patient populations. In recent years new direct acting antiviral agents (DAAs) have entered development. As HCV has a high mutation rate, combinations of DAAs with or without SOC are expected to be needed. The development path and regulatory guidelines for HCV DAAs are currently evolving as the first class of oral inhibitors are only now reaching Phase 3. Topics for discussion include the timing of nonclinical studies (including carcinogenicity), the need for combination toxicity studies, and what regional differences may exist (e.g. mitochondrial toxicity screening, environmental risk assessment).

Grushenka H. I. Wolfgang, PhD, DABT,
Dr. Wolfgang currently holds the position of Vice President of Drug Safety Evaluation at Gilead Sciences and has been responsible for the nonclinical development of early and late stage antiviral compounds at Gilead since 2002. Dr. Wolfgang received a M.S. in Pharmacology and Toxicology at Duquesne University and a Ph.D. in Pharmacology and Toxicology from the University of Arizona. She became a Diplomate of the American Board of Toxicology in 1992. Dr. Wolfgang worked at the Upjohn Company, Parke-Davis Pharmaceutical Research, and Chiron Corporation, before joining Gilead Sciences. At Chiron Corporation she began working on antiviral projects including development of small molecule inhibitors and vaccine candidates. At Gilead she has been involved in the development of HIV, HBV, HCV and HPV therapeutics.

Toxicological Considerations for Oligonucelotide Therapeutics
Page Bouchard, DVM, DACVP, Global Head of Preclinical Safety, Novartis

Oligonucleotide therapeutics are a diverse class agents that have as their common feature the fact that they are composed of nucleic acids (DNA, RNA, or chemically modified derivatives therof). Four major subclasses of oligonucleotide therapeutics in active development today are antisense oligonucleotides (ASOs), immunostimulatory oligonucleotides (ISOs), aptamers, and short interfering RNA (siRNAs). What primarily distinguishes the classes is the pharmacological mechanism of action. However, because of their common chemical composition, chemical synthetic processes and physicochemical properties, they have many potentially shared “class based” properties. Oligonucleotide class-based in vivo properties include metabolism by nucleases, and prototypical patterns of drug disposition, except when the oligonucleotide is chemically conjugated or encapsulated with other moieties that are designed to specifically modify drug disposition [polyethylene glycol (PEG), liposomes, etc.]. The rate of metabolism can be dramatically influenced by chemical modifications that impart nuclease resistance. Oligonucleotide class-based toxicological effects which

may be observed include, prolongation of coagulation times, activation of the alternative pathway of complement, activation of the innate immune system via interactions with Toll Like Receptors (TLRs), and uptakes and accumulation of drug-related material within certain prototypical tissues and cells. While these are all potential toxicological class-effects of any oligonucleotide therapeutic, the presence or potency of these effects can vary dramatically between molecules and therefore must be considered, but cannot be assumed. Other toxicological considerations will vary by subclass and several specific considerations will be reviewed for each of the major subclasses.

Oligonucleotide therapeutics are now being widely studied and dozens of product candidates in development today. Many of the overarching oligonucleotide class-based properties have been well established, but there remains unique considerations for each subclass and individual product candidate. These exciting new therapeutic candidates present interesting challenges for the drug safety scientist.

Page Bouchard, DVM, DACVP
Dr. Page Bouchard is currently the Global Head of Preclinical Safety for Novartis Institutes of Biomedical Research where he leads a group of over 400 associates responsible for the nonclincal safety assessment of Novartis products and product candidates around the world. Prior to joining Novartis, Page headed R&D at Archemix Corp., a privately held biotechnology company developing Aptamer therapeutics, a novel oligonucleotide therapeutic platform. Prior to Archemix, Page held positions as the Vice President of Drug Safety Evaluation at Millennium Pharmaceuticals, Assistant Vice President of Pathology at Wyeth, and Director of Preclinical Safety at Genetics Institute. Dr. Bouchard has over 15 years of Pharma/Biotech experience working on a diverse range of product types including recombinant human proteins and antibodies, small molecules, medical devices and oligonucleotide therapeutics. He received a bachelor's degree from Wesleyan University and a D.V.M. from Tufts University Veterinary School. He trained in veterinary pathology at Cornell Veterinary School, is Board certified in veterinary pathology by the American College of Veterinary Pathologists, and has served on the executive committee of the Society of Toxicologic Pathologists.

FDA and Nanotechnology for Medical Products
Richard A. Canady, PhD, DABT, Senior Advisor, McKenna Long & Aldridge, LLP

Drug developers must consider a wide range of issues when evaluating a decade long and extremely expensive approval process. Issues range from getting support to bring an idea to a stage where investors are interested in funding to determining what the best path forward would be to scale up, assure good manufacturing practices, and develop preclinical and clinical data. Some of the emerging issues to address are concerns such as environmental fate and effects of pharmaceuticals in the environment and whether and how FDA and EMEA will predictably express their data needs for evaluating safety and efficacy of a product that has nanoscale characteristics.

Nanoscale materials present a particular set of instrumentation and methodological challenges in demonstrating consistent manufacture to assure safety and efficacy as a marketed product. These challenges for nanomaterials convey a

sense of increased investment risk as FDA and EMEA must, essentially, develop methodological specifications sui generis for some nanoscale applications. The possibility of new instrumentation and data development methods conveys a sense that nanomaterials may take longer and be more expensive to bring to market. These perceived delays and uncertainties frighten off investors. However, balancing this increased investment risk is a potentially greater reward as transformatively new delivery and treatment methods are offered by nanomaterials. Understanding the policy and the science being considered at FDA and EMEA is essential in selecting products for development at this early stage in drug development using nanoscale materials.

Richard A. Canady, PhD, DABT
Richard A. Canady is a leading expert in regulatory risk assessment and nanotechnology regulatory policy having led multidisciplinary teams of policy and technical experts in the resolution of a wide range of cutting edge health risk management issues over a 20 year career that includes genomics, nanotechnology, biotechnology, obesity, contaminants in foods and medical products (including mercury, dioxins, perchlorate, and acrylamide), and medical product development.
Dr. Canady has a breadth of experience and insight in government regulatory policy for health risk assessment from the executive level, integrating across product review centers for the FDA Office of the Commissioner and across Federal Agencies for the Executive Office of the President. His experience includes substantial international work, leading policy and technical analysis teams within the Organization for Economic Cooperation and Development, the World Health Organization, and the Food and Agriculture Organization as well as in direct bilateral interactions with major U.S. trading partners on chemical risk management issues facing FDA.

Assessment of Genotoxic Impurities in Small Molecule Drug Candidates
Kurt Black, PhD, DABT, Comparative Biology Safety Science, Amgen.

The occurrence of genotoxic impurities in small molecule drug candidates is of increasing regulatory importance. Significant safety issues can arise from the presence of such impurities even at levels well below those typically requiring qualification by the conduct of toxicology studies. Furthermore, significant resources can be required to control genotoxic impurities below recognized limits. This talk will focus on the regulatory framework for genotoxic impurities and approaches to their identification, safety assessment and control. Considerations will be given to stage of development and clinical indication.

Kurt A. Black, Ph.D, DABT
Kurt Black is currently Scientific Director, Comparative Biology and Safety Sciences for Amgen Inc., where he oversees nonclinical safety assessment programs in the metabolic disorders therapeutic area. He also leads the development of the company's approaches to the toxicological assessment of impurities and metabolites and has served on numerous cross-functional teams developing company-wide strategies related to the chemistry, manufacturing and control of small molecule drugs. He has 20 years of experience in non-clinical safety assessment in the chemical, pharmaceutical

and biotechnology industries, including previous stints at Rohm and Haas Co., AztraZeneca Pharmaceuticals LP, and Merck and Co.

Safety Evaluation of Antibody Drug Conjugates
Kirsten Achilles-Poon, BS, Safety Assessment, Genentech

Antibody drug conjugates (ADCs), or immunoconjugates, are hybrid molecules usually comprised of monoclonal antibodies conjugated with potent cytotoxins, but also can consist of other molecules, such as antibody fragments or radioisotopes. Due to the promise of a targeted therapy and an improved therapeutic index compared to traditional chemotherapies, a number of ADCs are in clinical development for the treatment of a variety of cancers. Tumors that express specific antigens can be selectively targeted by the antibody portion of the ADC and, upon antigen binding, the cytotoxin can be internalized resulting in cell death. Ideally, to minimize off target toxicity, the target antigen would be over expressed in tumor compared to normal tissue. Since ADCs contain both biologic and small molecule components, standard approaches for pre-clinical safety evaluation for either component may not be appropriate or adequate and regulatory expectations are not well defined. Some challenges in designing pre-clinical toxicology programs include, but are not limited to: the selection of appropriate toxicology species, types of studies, determining the need to evaluate the safety of individual ADC components (e.g. un-conjugated antibody and free cytotoxin), development of pharmacokinetic assays, and assessment of the stability of the ADC and the potential release and toxicity of the free cytotoxin. Development strategies for ADCs, like biologics, are case-by-case and continue to evolve. Points to consider for the development of ADCs and case study examples will be discussed.

Kirsten Achilles Poon, BS
Kirsten Achilles-Poon is currently a Senior Toxicology Research Associate in Safety Assessment at Genentech, Inc. She received her Bachelors of Science degree in Biology from UCLA in 1989. In 1990, she began her career in the biotechnology industry working for Xoma Corporation as a researcher in the Toxicology/Pharmacology Department, which included designing and conducting GLP and non-GLP in vivo toxicology and pharmacokinetics studies, and included development of one of the first rodent continuous infusion models. In 1994, she moved to Genentech, Inc. to support the Pharmaceutical Research and Development Pulmonary Drug Delivery Group, where she conducted in vivo and in vitro studies to assess delivery and transport of inhaled biologics. After five years in this role, she moved into the Safety Assessment group to conduct and monitor investigational and GLP toxicology studies supporting the development of large and small molecule biologics. In her current role, Kirsten serves as a project toxicologist with a focus on antibody-drug-conjugates (ADCs). Kirsten has been involved in the pre-clinical development of ADCs for over ten years, including contribution to the IND filing of trastuzumab-MCC-DM1.

Incorporation of Fertility Endpoints in Non-Human Primate Chronic Toxicology Studies for Monoclonal Antibodies
Anu Vaidyanathan, Ph.D., DABT, Safety Assessment, Genentech

Historically, fertility assessment in non-human primate (NHP) general toxicology studies has been limited by availability of sexually mature animals. Therefore, stand-alone fertility studies have typically been reserved for late-stage development. However, there is industry and regulatory interest in identifying reproductive hazards earlier, especially for antibody therapies targeting non-life threatening diseases. To this end, incorporation of selective endpoints to assess fertility has been utilized in studies that include sexually mature monkeys. This is a case-by-case approach where the mechanism of action and patient population should be considered in the rationale. Incorporation of these endpoints in chronic toxicology studies may ultimately result in reduced animal usage and a more refined toxicology study design. Importantly, the most sensitive and high value fertility endpoints are readily incorporated into NHP general toxicology studies. An example of this includes histopathology on reproductive organs as well as additional measurements that will be described in further detail that can be collected to aid in screening. While traditional male fertility endpoints can be readily incorporated into a standard toxicology study design, we will discuss slightly different approaches to assess female fertility. In order to successfully use this approach, adequate identification of sexual maturity status at study onset is required. A weight of evidence rather than use of single endpoints may prove to be the most successful approach.

Overall, fertility assessment as part of NHP chronic toxicology studies may be considered adequate when no reproductive hazard is identified, or when a clear impact on fertility is identified that is consistent with mechanism of action. If reproductive toxicity is identified, follow-up studies may need to be designed to further characterize the specific insult as well as determine monitorability and reversibility. In addition, a high level overview of alternative strategies for fertility assessment will be discussed.

Anu Vaidyanathan, PhD, DABT

Anu Vaidyanathan is a scientist/toxicologist in the Safety Assessment Department at Genentech, Inc. Anu graduated from Northeastern University in Boston, MA with her PhD in Biomedical Sciences with a specialization in Toxicology. After graduation in 2003, Anu worked for 3 years at Sepracor Pharmaceuticals in the Boston area. At Sepracor, she worked on various small molecule projects targeting respiratory and CNS disorders, before joining Genentech in 2006. During her tenure at Genentech as a scientist in the Safety Assessment group, she has been the project toxicologist overseeing a number of large molecule programs targeting immunology indications such as rheumatoid arthritis, lupus, and multiple sclerosis ranging from early development to Phase III. She has also served as the project toxicologist on bio-oncology and antibody-drug conjugate early development programs. Additionally, Anu is a member of the Society of Toxicology and American College of Toxicology and is a Diplomat of the American Board of Toxicology.