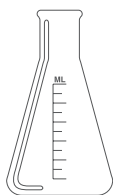


## Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

Volume 16, No. 2

Summer 2009

**Chair:** *Anna Nevius*

**Editors:** *David Henry, Jose Alvir, Deborah Panebianco*

## Note from the Editors

As medical science evolves, the methodology of clinical trials evolves to meet the new challenges. In this issue's feature article, Tai-Tsang Chen and Aparna Anderson discuss the new issues raised in oncology clinical trials and the new methods proposed to address these issues.

*News Flash:* The Biopharmaceutical Section is looking for biopharmaceutical statisticians who would like to talk about their industry/government/academic jobs. Videotaping will take place at JSM. If interested, please see the article "Hollywood Comes to JSM 2009" and respond immediately.

Other section news includes the section calendar, several upcoming conferences, the new section poster competition, and minutes of the section executive committee meeting.

We have several articles in the works for upcoming issues that we expect to interest you. They include propensity scores and their use in observational studies, and population pharmacokinetics and pharmacokinetics/pharmacodynamics. As always, we are open to suggestions for additional articles. ■

## Contents

### Featured Article

Novel Cancer Therapies: Issues to Consider in Designing Clinical Trials  
*Tai-Tsang Chen and Aparna B. Anderson . . . . 4*

### Biopharmaceutical Section News

Note from the Editors . . . . .	1
Letter from the Chair . . . . .	2
Biopharmaceutical Section Calendar . . . . .	11
Hollywood Comes to JSM 2009 . . . . .	12
FDA/Industry Workshop 2009 Open for Registration . . . . .	12
Biopharmaceutical Section Poster Award at 2009 JSM . . . . .	12
Highlights of the Biopharmaceutical Section Executive Committee Meeting . . . . .	13
65th Annual Deming Conference on Applied Statistics . . . . .	14
2009 Non-Clinical Biostatistics Conference . . . . .	15
Let's Hear from You! . . . . .	16

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## Letter from the Chair

I am very excited about all the things that the Biopharm Section is doing this year. You are invited to attend the Biopharm Business Section Meeting/Social at JSM. We plan to have reports about projects that we are pursuing, presentation of awards, socializing, and food. There will be a sign up sheet at the back if you would like to work on some of the projects that we are doing or suggest other projects that you would like to see happen. This is your section and we would like to promote projects that will benefit you.

The meeting announcement is given below:

### **Biopharmaceutical Section Annual Business Meeting and Mixer**

**Date:** Tuesday, 8/4/2009

**Start Time:** 5:30 PM

**End Time:** 7:00 PM

**Room Name:** CC-207B

CC=Walter E. Washington Convention Center

One project that we are working on is a Member Survey. Ram Suresh and his committee members, Tom Lin, Iksung Cho, and Ed Luo have finalized the survey and are exploring ways to implement it. Watch for further news.

Steve Gulyas is working with Jeremy Jokinen to get us moving on the web-based interactive outreach project to interest students in statistics as a career. There is an article in the bulletin about the project and a request for help.

I have noticed in talking with fellow statisticians and in interviewing candidates for statistical jobs that many people do not realize that the Center for Veterinary Medicine (CVM) is one of the components of the Food and Drug Administration. I would like to take this opportunity to tell you a little about CVM, one of the smallest Centers in FDA. I have worked here for over 24 years and find it challenging and exciting.

CVM is a consumer protection organization like the rest of the Centers in FDA but our mission is to foster public and animal health by approving safe and effective products for animals and by enforcing other applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities. When a drug is approved for use in food-producing animals, not only must the safety to the animal be demonstrated, but also the safety of food products for human consumption.

To accomplish its mission, CVM uses a number of methods to evaluate the safety and effectiveness of animal drugs. These methods are reviewed and analyzed by the statisticians at CVM.

Our Center is composed of the Office of New Animal Drug Evaluation, Office of Research, and Office of Surveillance and Compliance as well as Office of the Director and Office of Management. Our group of 13 statisticians (when fully staffed) works mostly with the Office of New Animal Drug Evaluation but does do some consulting with the Office of Research and the Office of Surveillance and Compliance. Below is a brief description of the three offices mentioned.

*The Office of Surveillance and Compliance* is the enforcement part of our Center. It coordinates inspections and collects reports of adverse drug reactions from the use of veterinary drugs in animals. The Biostatistics group works with this office in developing sampling plans, questionnaires, and other studies.

*The Office of Research* conducts Center-driven applied research necessary to establish and support Agency policies in regulating animal drugs, feed additives, and veterinary devices. This office conducts research in analytical and residue chemistry, toxicology, pharmacology, immunology, microbiology, and nutrition. The Biostatistics group works with the researchers in designing and analyzing their studies.

*The Office of New Animal Drug Evaluation* reviews information submitted by drug sponsors who desire to obtain approval to manufacture and market animal drugs. Before an animal drug receives FDA approval, it must be tested for effectiveness and safety. The Biostatistics group works with the veterinarians, animal scientists, chemists, and toxicologists in reviewing protocol designs for safety and effectiveness studies and in evaluating safety and effectiveness studies submitted by the pharmaceutical industry as part of the approval package.

The subjects in our studies are animals rather than people. Thus, we have many species to work with and none of them can speak for themselves. We liken this to evaluating infants and adults with advancing stages of dementia. As you will see from the description below, we have studies with few animals. However, we also have studies with large numbers of animals but very small numbers of experimental units. For example, in reviewing fish data, the fish are housed in tanks and all fish in the tank are given the same treatment. Thus we have lots of fish but only as many experimental units as there are tanks, usually a number much less than 50. In addition, to survive fish need flowing water. The number of independent units becomes even fewer if more than one tank is supplied water from the same source and the drug is administered in the feed or water. We have three broad classes of drugs and these are described below, therapeutics for non-food animals, therapeutics for food animals, and production drugs.

*Therapeutics for non-food animals:* Drugs used in companion animals (cats, dogs, and horses), wildlife, and domestic non-food animals to prevent, treat, or control diseases are known as therapeutic drugs for non-food animals. This is the category most similar to human medicine because there are no food-safety concerns. “Non-food animal” is a general term for any animal that is not part of the food chain. We evaluate data concerning a variety of diseases and/or conditions, such as those that affect the following systems: cardiovascular, digestive, musculoskeletal, reproductive, nervous, respiratory, integumentary, urinary, eye and ear. There is a need for safe and effective antimicrobial and antifungal agents, antiparasitic agents, anesthetics and analgesic drugs, and steroids, just to name a few.

The sample sizes of studies we review are often very small, which make the proper use of statistics paramount. For example, in studies involving binomial parameters, such as treatment success, many times we make decisions with sample sizes of around 100 per treatment group.

Another major difference from other parts of FDA is that we are able to test products and drugs in the target species at every stage of development. For safety studies, this means that we are evaluating toxicity studies in the target species. This is true for all the animal drugs that we evaluate. However, we also evaluate rat and mice studies to test for carcinogenicity.

*Therapeutics for food animals:* Drugs used to prevent, treat or control disease in livestock, poultry, and fish are classified as therapeutic drugs for food animals. Most of these animals are housed in large groups. When diseases occur in these settings, typically a whole pen of animals may be treated. Through the use of toxicological findings and residue chemistry studies a determination is made regarding the upper, or safe limit of a new animal drug residue in the edible tissues of a food animal. This includes establishing a tolerance and, if appropriate, a withdrawal period. Because food animals are generally raised in controlled settings, we have more control in designing the experiment. Many of our studies are randomized complete block designs run at multiple locations.

*Production drugs for food animals:* Drugs used to enhance food production or value, rather than treat diseases, are known as production drugs for food animals. There are four major groups of food animals involved—swine, beef cattle, dairy cattle, and poultry. Production animal drugs are given to normal, healthy animals to enhance their ability to produce meat, milk, or eggs or to enhance the quality, e.g., lean pork. These drugs are usually given in the feed, by ear implantations, or by injection.

Because production drugs are given to entire groups of animals, many of our studies are randomized complete block designs run at multiple locations. Example of the types of effectiveness variables measured for production are weight gain, feed efficiency, carcass leanness or increase in milk production. While these variables are continuous and easy to measure, they present challenges in analyses because the detectable differences between the treatment and control groups are generally in the 1-3% range.

*Withdrawal time for food production drugs:* Withdrawal time is the length of time that must elapse after a food animal is exposed to a drug before it can be sold at the marketplace for consumption. The Biostatistics group is involved in analyzing the data from drug residue trials used to set the withdrawal times.

Thanks for letting me share my work with you.

I am looking forward to seeing you at JSM in DC in August. ■

# Novel Cancer Therapies: Issues to Consider in Designing Clinical Trials

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## Introduction

Over the last few decades, innovative laboratory research has led to the discovery of many promising targeted anti-cancer agents. These include selective or multi-targeted inhibitors of tyrosine kinases, signal transduction, angiogenesis, or matrix metalloproteinase as well as targeted immunotherapies such as monoclonal antibodies, T cell infusion, and cancer vaccines. The ever-increasing number of potentially active compounds and the varying mechanisms of action raise important questions that challenge the current preclinical and clinical drug development paradigm. What is the most efficient way to advance the development of these novel agents while minimizing the chance of discarding potentially effective therapies? Do the conventional efficacy and safety endpoints and trial designs adequately address the new mechanisms under study?

Cytotoxic and cytostatic agents are classified based on their mechanism. Classical cytotoxic agents derive their anti-tumor activity from dose-dependent rapid cell kill. However, their lack of selectivity between normal and cancerous cells usually results in undesired toxicities or side-effects. Cytostatic compounds are agents that are designed to inhibit or suppress cellular growth and division. Some of the characteristics of the cytostatic compounds include minimal or less severe toxicity, prolonged duration of the treatment, anti-tumor activities at potentially low doses, and inhibition of tumor growth with absence of or minimum tumor shrinkage.

Immunotherapies, on the other hand, stimulate the patient's own immune system to react against the cancer by targeting antigens expressed on cancer cells or molecules that are necessary for tumor growth. Monoclonal antibodies, produced by injecting proteins from human cancer cells into mice, represent a significant subset of immunotherapy agents being used to treat cancers. Monoclonal antibodies bind to antigens specific to the cancer cell which in turn induces or enhances an immune response against the targeted cancer cell. In certain cases, the binding of an antibody to a cancer cell produces inhibition of a growth pathway, rather than an immunologic effect.

Historically, the development of cytotoxic agents has progressed from the early phase studies assessing safety to later phase studies evaluating efficacy (Friedman, et al., 1998). The design of these clinical trials has been well established. The goal of the phase I studies is dose-finding. The side-effects and the pharmacokinetics of an agent are assessed and the maximum tolerated dose (MTD) or the recommended phase II dose is determined by identifying the dose limiting toxicity (DLT). The dose is then carried forward to subsequent phase II studies to evaluate the potential anti-tumor effect. If the agents under investigation are deemed sufficiently efficacious to warrant further investigation, large phase III randomized clinical trials are performed to confirm clinical benefit. This traditional development paradigm can also be used to assess novel cytostatic agents and immunotherapies, especially those that may reduce tumor burden. However, with potentially different toxicity profiles and different mechanisms that induce anti-tumor activity, conventional endpoints and/or study designs may not allow the optimal means for evaluating clinical efficacy and safety for these new classes of cancer therapies.

In this article, we will use 'cytostatic agents' to refer to the compounds of which the primary mechanism is to inhibit tumor growth, while 'cytotoxic agents' are agents that induce tumor shrinkage through direct tumor cell kill. Immunotherapies, which might inhibit growth or shrink existing tumors, will also be addressed. We will give a brief review of the existing methodology used in the evaluation of cytotoxic agents and consider the potential adaptation of these methods in the assessment of novel agents. The purpose is not to recommend certain methods over others, but to provide an introduction to study designs and endpoints that have been considered in the development of cytostatic and immunotherapeutic agents. More importantly, we would like to raise awareness among

statisticians that one size does not fit all. It is essential to fully understand the characteristics of the compounds under investigation to determine the appropriate trial design and selection of the best endpoint.

## Phase I trials

Phase I studies of cytotoxic agents are performed to determine the recommended phase II dose (RP2D) by identifying dose limiting toxicities (DLT), and the maximum tolerated dose (MTD). The objectives of these phase I studies are usually to evaluate the toxicity profile using the Common Toxicity Criteria (CTC), to understand the pharmacodynamics and pharmacokinetics of the compound, and to have an early assessment of activity from the different doses administered. It has been a general rule that the dose administered should be as high as possible in order for a cytotoxic agent to achieve maximal tumor reduction.

The development of cytostatic agents in phase I studies is similar in that the goal is to identify the RP2D with acceptable side-effects. However, defining the MTD is more challenging since the wide dosing range that might demonstrate efficacy may not result in identification of the MTD. In other words, the drug concentration required to inhibit the targets may not be the one that induces an unacceptable toxicity.

Furthermore, an important consideration is the selection of the patient population. The patients enrolled in the traditional phase I studies with cytotoxic agents tend to be heavily pretreated, multiple refractory end-stage cancer patients. These patients usually have worse prognoses and tend to withdraw from the phase I study relatively quickly due to disease progression or study drug intolerance. In contrast, the toxicities observed in phase I studies of cytostatic agents are usually limited, and the efficacy is often observed only after prolonged administration of the treatment. In studies of cytostatic agents, it becomes necessary then to enroll patients who are sufficiently healthy to stay on study long enough to have a preliminary assessment of both efficacy and of the long-term safety profile. This in turn suggests that the traditional algorithm-based '3+3' design (Lin et al., 2001) might not be appropriate in the evaluation of the cytostatic agents.

Other dose-finding phase I trial designs such as the Continual Reassessment Method (CRM) and several of its variations have been proposed (O'Quigley et al., 1990, 1996, 1998; Faries, 1994; Møller, 1995; Goodman et al., 1995; Legedza et al., 2000). Storer (2001) provides a thorough evaluation of phase I trial designs in the continuous dose-response setting. Despite the wealth of trial designs that has existed, most operate under the objective of finding the MTD.

Therefore, in addition to determining the MTD using conventional phase I methods, cytostatic agents usually require further investigation to determine the optimal biological dose (OBD), i.e., the dose level at which these agents achieve the maximum target inhibition and thus potentially, their clinical effect. However, the use of target inhibition as a potential measurement in defining the OBD implies a complete understanding of the target under investigation. Due to biologic complexity, this is no easy task. Even if the biological pathway is clearly identified, target inhibition can only be viewed as a biological marker. More research will be required to validate its correlation with the endpoints that are related to the improvement of patient benefits. Another potential endpoint for dose finding could be drug concentration in the blood, or better, in the tumor. This, too, requires further validation.

With immunotherapeutic agents, an association between efficacy and immune-mediated toxicity may be observed, but the mechanism of these compounds does not necessarily support the idea that the maximum tolerated dose yields the greatest efficacy. Moreover, because the body's own immune system is triggered to combat the disease, establishing the optimal dosing schedule is often challenging. Trial designs that utilize a dose-finding strategy based on efficacy and safety monitoring (Thall et al., 1998, 1999, 2006) could be considered in this setting.

*The purpose is not to recommend certain methods over others, but to provide an introduction to study designs and endpoints that have been considered in the development of cytostatic and immunotherapeutic agents.*

## Phase II trials

The goal of conventional phase II clinical trials is to evaluate the anti-tumor activities of a new drug or a new treatment regimen usually by assessing the objective tumor response rate. Single-arm phase II clinical trials are undertaken to establish whether a new agent has sufficient activity to warrant further investigation. When a study is designed to obtain a more precise estimate of the anti-tumor activity, such as objective tumor response rate, it is usually called a phase IIA study, whereas a phase IIB study is performed to formally test the level of clinical activity with a new agent, either in a single-arm or a randomized comparative setting.

While phase II designs for evaluating cytotoxic compounds can be applied to the cytostatic and immunotherapeutic agents, the primary endpoint in studies of target-based agents should allow assessment of inhibition or delay of tumor growth in addition to reduction in tumor size (i.e., objective response). Some of the potential endpoints in the phase II trials that might be considered include disease control rate, defined as the rate of complete (CR) and partial response (PR), and stable disease (SD); major durable disease control rate, defined as the rate of disease control lasting greater than a clinically meaningful length of time (e.g., 6 months); and progression-free survival rate.

Conventional response criteria (e.g., RECIST or WHO) may also need to be revisited when studying mechanisms of action that differ significantly from classical paradigms. Unlike cytotoxic agents, the kinetics of response with certain immunotherapies might not preclude tumor shrinkage following conventional definitions of progressive disease. In some cases, the so-called disease progression may in fact be due to T cell infiltration of tumors leading to the appearance of growth, while in other cases new lesions may be observed concurrently with the shrinking of target lesions. With such agents, the schedule of tumor assessments needs to be carefully considered, and the definition of disease progression may need to be modified to reflect overall tumor burden at a given time, including new lesions (Hamid et al., 2007).

When the primary outcome of interest is binary, phase IIA and IIB trial designs have been well established for estimation and hypothesis testing, respectively. The sample size in the phase IIA study is often specified along with its maximum width of the confidence interval. For example, given a sample size of 20, the maximum width of the confidence interval is 45.6% if the observed success rate is 50%. Chen, Iyer and Anderson (2007) proposed a simple phase IIA trial design based on the width of confidence interval when the endpoint of the study is a binary outcome such as the objective tumor response rate. The sample size is determined such that the probability that the confidence interval width is smaller than a pre-specified small value, given the confidence interval covers the true underlying success rate, is greater than a pre-determined threshold. Multiple-stage designs of phase IIA studies are also available (Gehan, 1961).

Several phase IIB designs, including single stage or multiple stage designs, have been proposed (Fleming, 1982; Simon, 1989; Ensign et al. 1994; A'Hern, 2001) based on hypothesis testing. The focus of these methods is to obtain the sample size by fixing the maximum tolerable type I and type II errors. Other authors such as Korn et al. (2001) and Simon et al. (2001) proposed a phase II.5 design that resembles the usual phase III studies but with higher type I error rate, e.g., 20%, and/or larger than anticipated estimates of treatment difference. They cautioned that the use of a larger type I error rate means that such trials cannot serve as the confirmatory studies, and larger definitive follow-up studies are needed.

As mentioned earlier, prioritization of new treatments for phase III evaluation becomes crucial given the large number of agents under evaluation. Agents with higher potential need to be identified and those that are not efficacious need to be discarded at the earliest stage of development. In traditional drug development, the candidates are typically evaluated in separate phase II clinical trials. Although this approach is fundamentally sound, considering each agent in isolation has major drawbacks, including prolonged development duration, increasing financial burden and lack of parallel evaluation among compounds with similar mechanisms. To maximize the benefits, several study design alternatives, such as randomized screening designs, multiple-stage or group sequential study designs, can be considered.

The use of a randomized phase II design for selecting a treatment among many potential candidates was first introduced by Simon et al. (1985). Eligible patients are randomized among treatments, and the treatment with the most favorable point estimate in the endpoint of interest is selected for further testing. The design usually yields an acceptable sample size and is easy to implement. However, results of these randomized phase II studies should be considered

as pilots to further definitive evaluations. Liu et al. (1999) showed that the false-positive rates could range from 20% to 40% in multiple-arm selection designs. Similar designs were also proposed by Thall et al. (1988, 1989).

Several other authors proposed a formal way to perform screening experiments. Using Bayes empirical formulation, Yao et al. (1996) considered a study design in which the individual sample sizes are optimized to minimize the time to identify a promising agent with fixed error rates. This approach was later extended to multiple-stage designs or sequential designs in the same setting (Wang et al., 1998, 2001; Yao et al., 1996, 1998).

Although binary outcomes such as disease control rate can be used in the primary assessment of anti-tumor activities for cytostatic agents, those patients who do not have enough follow-up by the time of the analysis are usually considered as treatment failures. For this reason, another alternative that has gained the attention of clinical researchers is the evaluation of overall survival (OS) or progression-free survival (PFS) in phase II studies. Such studies also provide a closer link to the primary endpoint that would be considered in the phase III development. Mick et al. (2000) examined a design that evaluates clinical benefit by comparing sequentially measured paired failure times within each patient. Other authors have also proposed multiple-stage designs of phase II cancer trials using time-to-event analyses (Lin et al., 1996; Case et al., 2003). Some of the issues when monitoring time-to-event endpoints in the early clinical trials are discussed by Cheung et al. (2002) and Thall et al. (2005).

Also gaining more attention are enrichment designs such as randomized discontinuation design (Kopec et al., 1993; Rosner et al., 2002). All patients receive the agent under investigation in the first stage. After a specified duration of follow-up, those who benefited from treatment (e.g., those who are progression-free) are randomized to either continue treatment or receive placebo. In the settings where a standard cytotoxic agent is combined with a novel cytostatic agent, patients could be randomized to receive cytotoxic agent with or without the cytostatic agent in the second stage of the study. The intent is to increase the homogeneity of the patient population and isolate the population in which the patients will receive the maximum benefit of the treatment. Although restricting randomization to a more homogeneous population allows maximization of the statistical power, Capra (2004) showed that the loss of information in subjects who are enrolled and not randomized in the randomized discontinuation design is of sufficient magnitude, resulting in loss of power compared to the classical randomized design with time-to-event endpoints. Freidlin et al (2005) also reached a similar conclusion. While they state the development of cytostatic and immunotherapeutic agents could benefit from the use of the randomized discontinuation design with careful planning, they show that the randomized discontinuation design is not as efficient as the traditional upfront randomization design when the treatment has a fixed effect on tumor growth or if the treatment benefit is restricted to slower-growing tumors.

*To maximize the benefits, several study design alternatives, such as randomized screening designs, multiple-stage or group sequential study designs, can be considered.*

## Phase III trials

Phase III study designs with cytostatic agents are generally no different from the traditional studies involving cytotoxic agents, with a focus on assessing treatment benefit risk profile. For the primary objective of demonstrating efficacy, improved overall survival is generally considered the ultimate evidence of clinical benefit and is therefore considered the gold standard among efficacy endpoints. However, other endpoints such as progression-free survival or, in the adjuvant setting, disease-free survival are often chosen as biological endpoints for overall survival (Biomarker Definitions Working Group, 2001), although with some immunotherapies the definition of progression may require some modification from conventional criteria, as noted above. Methods exist to quantify the proportion of treatment effect explained by such markers (Lin et al., 1997; Li et al., 2001).

The strategy of bringing a cytostatic agent directly from phase I to phase III is becoming more commonplace, especially when there is preclinical evidence of drug activities and biomarker confirmation of pharmaceutical effect.

When a phase III oncology study is planned without sufficient and robust phase II efficacy data, an interim futility analysis that takes on the role of decision-making to transition from phase II to phase III is desirable. Ellenberg et al. (1985) proposed a phase III design that allows for early study termination in the face of negative trend based on the binary outcome. The study may be terminated if the response rate of the experimental agent is the same or smaller than that of the control arm in the phase II stage. Wieand et al. (1994) and Chen et al. (2009) generalized their approach to time-to-event endpoints. Inoue et al. (2002) also proposed combining phase II and phase III within a single trial using a Bayesian framework. Stallard and Todd (2003) considered a trial design in which the most promising of a number of experimental treatments is selected at the first interim analysis. This allows a phase III study to include the treatment selection element of a phase II study. The study design shortens the development time line by screening multiple agents in the first stage of the phase III study. Similar suggestions have also been made by others (Schaid et al., 1990; Bauer et al., 1995; Posch et al., 2005; Liu et al., 2005). However, a phase II/III design also has some important limitations. For example, an external group (e.g., a Data Monitoring Committee) is entrusted with the decision to move to phase III, and only limited refinement of phase III is possible based on the results of the phase II component.

Another element of trial design that is critical to the understanding of clinical activity with cytostatic and immunotherapeutic agents is the identification of subset populations in which tumors show over-expression of targets. Simon and Maitournam (2004, 2005) proposed phase III targeted clinical trial designs that are tailored for the population that is expected to show response. They evaluated the relative efficiency of a targeted clinical trial design to an untargeted design for a two-arm randomized clinical trial in the context of a binary outcome endpoint. The two designs were compared with respect to the total randomized subjects required. Also, the number of randomized subjects in the untargeted design was compared to the number of screened subjects required for the targeted design. The authors examined different scenarios of treatment effect in responsive and non-responsive subsets and concluded that the targeted trial designs can be efficient and the number of patients needed can be dramatically reduced when the mechanisms of the agents are well understood and the accuracy of the assay used in the prediction of responsiveness is high.

## Summary

This article offers a review of the trial designs and endpoints for all phases of development that have been proposed for both cytotoxic and cytostatic agents. Also summarized are some of the challenges researchers face in the development of cytostatic agents and immunotherapies.

Clearly the objectives of phase I, phase II and phase III studies remain the same in the development of cytostatic and immunotherapeutic agents. Instead of abandoning the existing methodology developed to evaluate cytotoxic agents, the introduction of the cytostatic agents calls for modification of these traditional trial designs. However, much work remains to be done. Parulekar et al. (2004) reviewed 60 publications of phase I studies in which targeted, non-cytotoxic agents were examined. Of the 60 completed phase I studies, they found that the majority of the study designs were toxicity-based, and a small portion of the studies used pharmacokinetic data as endpoints in the selection of the RP2D. According to the authors, the challenges that must be overcome include defining cellular or signaling pathways and developing reliable assays for the drug effect measurement.

With so many oncology compounds under development having novel mechanisms, statisticians are being challenged to propose alternatives to the conventional study designs. The 'one-size-fits-all' drug development paradigm is no longer applicable in the era of increasing non-cytotoxic agents. To bring an effective treatment to patients in an efficient but safe manner, statisticians must proactively collaborate with clinicians in this process. To this end, clinical trial statisticians will need to understand the mechanisms of the compounds under investigation, help clinicians understand the potential limitation and advantages of statistical designs and definitions of endpoints, stay abreast of current and new methodologies, and interact with the statistical community at large to benefit from the experience of others.

## Acknowledgements

The authors are grateful to Dr. Renzo Canetta, Dr. Dominic Labriola and Dr. Zhengqing Li for providing their comments that led to significant improvement of this article.

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## Biopharmaceutical Section Calendar

- July 23, 2009**      **Webinar: Large-scale Significance Testing of Genomic Data**  
John Storey (Princeton University)  
Noon – 2 pm (Eastern Time)  
<http://www.amstat.org/sections/sbiop/webinarseries.html>
- August 24, 2009**      **Webinar: Genomic Data Analysis with Targeted Maximum Likelihood and Super Learning**  
Mark van der Laan (UC Berkeley)  
Noon – 2 pm (Eastern Time)  
<http://www.amstat.org/sections/sbiop/webinarseries.html>
- August 1–6, 2009**      **Joint Statistical Meetings**  
Washington Convention Center  
Washington, DC  
<http://www.amstat.org/meetings/jsm/2009/index.cfm>  
Biopharmaceutical Section Business Meeting and Mixer  
Tuesday, August 4th, 5:30-7:00 pm  
Room CC-207B in Washington Convention Center
- Sept. 23–25, 2009**      **FDA Industry Workshop**  
Capitol Hilton  
Washington, DC  
<http://www.amstat.org/meetings/fdaworkshop>  
<http://fdaindustry09.blogspot.com>
- Oct. 21–23, 2009**      **2009 NCB Non-Clinical Biostatistics Conference**  
Harvard Medical School  
Boston, MA  
<http://www.ncb2009.org>
- Dec. 7–11, 2009**      **65th Annual Deming Conference on Applied Statistics**  
Tropicana Casino Resort  
Atlantic City, NJ  
<http://www.demingconference.com>
- March 21–24, 2010**      **ENAR 2010 Spring Meeting**  
Hilton New Orleans Riverside  
New Orleans, LA  
<http://www.enar.org/meetings.cfm> ■

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## Hollywood Comes to JSM 2009!

**Jeremy Jokinen and Steve Gulyas**

The Biopharmaceutical Section is completing a web-based interactive outreach initiative intended to recruit students and young professionals into careers in biopharmaceutical statistics. The final product will be a website that includes video interviews of current statisticians discussing various aspects of their jobs; video clips may also be used for distribution at career fairs and other Biopharm-supported venues. If you would like to nominate someone (including yourself!) to be in these videos, please forward their name to Jeremy Jokinen ([jjokine1@its.jnj.com](mailto:jjokine1@its.jnj.com)) by July 24, 2009. We would like to consider individuals at all levels of career development and from different settings (eg, FDA, academia, industry). The only restriction is that we will shoot video at JSM 2009, so all nominees must be planning to attend the meeting and willing to make themselves available for interview during the meeting. For those that are camera shy, there will be a demonstration of the services that the Biopharm section has enlisted during the business meeting on Tuesday, August 4. ■

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## FDA/Industry Workshop 2009 Open for Registration

The FDA/Industry Workshop 2009 is a practical conference planned by and for statisticians in the FDA, Industry and Academia.

This year's workshop is held in downtown Washington D.C. on September 23–25. Eight short courses are offered. For more information and registration, please visit <http://www.amstat.org/meetings/fdaworkshop/>. ■

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## Biopharmaceutical Section Poster Award at 2009 JSM

**Yongming Qu, Chair of Biopharmaceutical Section Poster Award**

Back in January 2008, the Biopharmaceutical Section asked for ideas to promote biopharmaceutical statistics. One of the emergent ideas was to set up a poster competition to recognize the significant work for presenting the posters, increase the number of posters, and improve the quality of the posters at JSM. Jingli Song, a Lilly colleague, and I were immediately fascinated by this idea, because posters, which do not have a tight limitation on the time for presentation, allow audiences to have full interaction with the presenters. We submitted a proposal to the Biopharmaceutical Section Executive Committee to establish the poster competition. Soon the proposal was approved! The Biopharmaceutical Section Poster Award Committee was formed with three members: Chair: Yongming Qu, Members: Jingli Song and Junyuan Wang. The charter was finalized and approved by the Pharmaceutical Executive Committee in August 2008. Monica Clark, Daniel Christen and Neal Thomas helped advertise the poster competition by sending an email to Biopharmaceutical Section members, posting an announcement at [www.amstat.org](http://www.amstat.org) and publishing an announcement in the October 2008 issue of *Amstat News*.

By May 1, 2009, the deadline for authors to submit the final posters for competition, we received 12 qualified posters. It happened that no one from Lilly and Wyeth submitted posters, so we selected all referees from these two companies in the absence of conflict of interest. Each poster was reviewed by 2 referees, and total scores based on the two referees were assigned to each poster. The evaluation was based on four criteria: innovation, general

applicability in pharmaceutical research, appropriate example(s), and effectiveness of presentation (well written, well organized, etc). The first, second and third place winners were selected based on the total scores. The committee reviewed the three winning posters and all felt they were well deserved. Stay tuned for the announcement of the three winners at JSM. You can either learn about it at the Biopharmaceutical Section mixer or look for ribbons around the posters! We also welcome everyone to participate in the 2010 poster competition.

In the end, I would like to thank the Poster Award Committee, the Biopharmaceutical Section Executive Committee, the poster referees, and poster competition participants for their support. I would also like to express my special thanks to Steve Gulyas, who helped this initiative in numerous ways from the very beginning. ■

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## Highlights of the Biopharmaceutical Section Executive Committee Meeting, Washington, DC, November 7, 2009

**Kannan Natarajan, Past-Chair**

—Steve Gulyas discussed a proposal from a vendor who would help design a Biostatistics Outreach web site. Steve will write a requirements document.

—Steve Gulyas gave the Treasurer's report. The Section has a healthy balance. The Executive Committee agreed to host a mixer at the 2009 FDA/Industry Workshop, but we will not host a reception at ENAR.

—Steve Gulyas reported from the New Initiatives Subcommittee that the JSM poster award is moving forward, and it will be announced in the *Amstat News*.

—Matilde Sanchez, JSM Program Chair, reported that there will be 6 invited sessions at 2009 JSM, which is the maximum available. The Biopharmaceutical Section has endorsed 3 or 4 short courses.

—Mani Lakshminarayanan outlined the plans for future web-based training sessions.

—Jeff Maca reported that the 2008 FDA/Industry Workshop was well-organized and well-attended.

—Tammie Massie reported that they are looking for a larger venue for the 2009 FDA/Industry Workshop. ISBS may participate.

—David Breiter gave the Council of Sections report. Both of the proposed new sections were approved:

- Section of Statistical Programmers and Analysts
- Section on Data Mining

—Christie Clark submitted the Student Paper Competition announcement, which appeared in the *Amstat News*.

—Ram Suresh, Chair of the Membership Committee, reported that the membership survey was completed; and the 2009 survey is on track for distribution. ■

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## **65th Annual Deming Conference on Applied Statistics ASA Biopharmaceutical Section & ASQ Statistics Division December 7-11, 2009; Atlantic City, NJ**

The purpose of the three-day Deming Conference on Applied Statistics is to provide a learning experience on recent developments in statistical methodologies. The conference is followed by two parallel short courses on (1) Analysis of Clustered Categorical Data by Profs. Alan Agresti; University of Florida and Bernhard Klingenberg; Williams College; and (2) Statistical Evaluation of Surrogate Endpoints in Clinical Trials by Prof. Geert Molenberghs, I-BioStat, Universities of Hasselt & Leuven. The conference is composed of twelve three-hour tutorials on current statistical topics of interest. Recognized experts in the field of applied statistics have been invited to give the lectures and short courses based on their recently published books. The conference makes the eight books for this year available for sale at an approximately 40% discount. Attendees will receive bound proceedings of the presentations. The full program and online registration is available on [www.demingconference.com](http://www.demingconference.com). The conference will be held in the state-of-the-art Havana Tower of the Tropicana Casino Resort. Walter Young has chaired this conference for 40 consecutive years. ■

# 2009 NCB

Harvard School of Public Health  
Boston, Massachusetts



October 21 - 23

## Non-Clinical Biostatistics Conference

Under the theme of *Statistical Methodologies: Key to Discovery, Safety Assessment and Development*, this conference will bring together members of the non-clinical/pre-clinical statistics community to discuss scientific and regulatory issues, to network and to share experiences.

### **PROGRAM:**

- Half-day short course on *Longitudinal Data Analysis* (by Garrett Fitzmaurice).
- Presentations and posters covering the following broad subject areas:
  - Discovery/Early Development/-omics
  - Pharmacology/Safety/Toxicology/pK
  - CM&C/Manufacturing
  - General Methodology
- Welcome reception and conference dinner

### **INVITED SPEAKERS:**

- ShaAvhree Buckmann (FDA; Keynote Speaker)
- Keith Baggerly (M.D. Anderson Cancer Center)
- Emery Brown (Harvard-MIT)
- Dan Holder (Merck)
- Ralph Kodell (FDA)
- John Peterson (GSK)
- Steve Ruberg (Lilly)
- Dennis Sandall (Siegfried)
- Terrence Tougas (Boehringer)

#### *Organized Jointly By:*

The Non-Clinical Biostatistics Leaders Forum and The Program for Quantitative Sciences in Medicine, Department of Biostatistics, Harvard School of Public Health

#### *With Support From:*

Biopharmaceutical Section of the American Statistical Association, Adolphe Quetelet Society, a section of the International Biometric Society, and the National Institute of Statistical Sciences (NISS)

### **DATE:**

October 21-23, 2009

### **LOCATION:**

Joseph B. Martin  
Conference Center  
Harvard Medical School

Visit our website,  
[www.ncb2009.org](http://www.ncb2009.org), for  
registration information and  
abstract submission.

Deadline for Contributed  
Presentations is  
**July 1, 2009.**

Please direct questions to:  
[info@ncb2009.org](mailto:info@ncb2009.org)

## Let's Hear from You!

If you have any comments or contributions, please contact the Editors: David Henry, phone 609-818-4142, email [david.henry@bms.com](mailto:david.henry@bms.com); Jose Alvir, email [Jose.Alvir@pfizer.com](mailto:Jose.Alvir@pfizer.com); Deborah Panebianco, email [deborah\\_panebianco@merck.com](mailto:deborah_panebianco@merck.com).

We are looking for volunteers to write articles that will be of interest to our members. Some authorless topics that have been suggested include bioequivalence in biologics and personalized medicine. If you have been working in an area and would like to suggest a topic or volunteer to write, please send us an email. Non-technical articles related to our work are welcome. One example might be an article about outsourcing statistical programming to Asia. Perhaps someone could write an article about how to effectively work when the statistical programming is outsourced. How is it different from using a regular CRO? How will our function change?

*The Biopharmaceutical Report* is a publication of the Biopharmaceutical Section of the American Statistical Association.