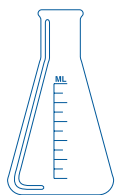


## Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

Volume 10, No. 2

Winter 2002

**Chair:** *Bob D. Small*

**Editors:** *Kevin W. Anderson, Neal Thomas, and Kannan Natarajan*

## Forward

**Kevin W. Anderson, Kannan Natarajan, and Neal Thomas**

Statistical Analysis Plans (SAPs) are documents whose creation occupies much of a pharmaceutical statistician's time. Statisticians in other industries are often surprised to learn the extent of the pre-specification of analyses that occurs, often before data are available to serve even as training samples. Nevertheless, unlike other areas, prospectively pre-specifying the analyses prior to data lock and unblinding of treatment assignments is perceived to minimize bias, especially when assessing the efficacy of an experimental drug. This has been a requirement by most regulatory authorities worldwide as part of regulatory compliance. Despite their central role in pharmaceutical clinical trials, SAPs appear to receive little attention in statistical texts and articles; for example, there are no entries on analysis plans in the Encyclopedias of Statistics, Biostatistics, or Biopharmaceutical Statistics. The ICH guidelines on "Statistical Principles for Clinical Trials" describes SAPs as:

"The statistical analysis plan may be written as a separate document to be completed after finalising the protocol. In this document, a more technical and detailed elaboration of the principle features stated in the protocol may be included. The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of data and should be finalised before breaking the blind. Formal records should be kept of when the statistical analysis plan is finalised as well as when the blind was broken."

Although the ICH guidelines contain subsequent recommendations about statistical topics to be included in the protocol, there are numerous opinions about the level of detail appropriate for statistical sections of protocols and SAPs. The recent experience of the *Biopharmaceutical Report* editors and their colleagues has been for more detailed SAPs completed at earlier stages of studies. This push has come from within corporations as part of the continual effort to reduce the time allocated to complete studies following last-patient-last-visit. Detailed pre-specified SAPs for integrating Phase III efficacy and safety data are also becoming common as a means of accelerating time to submissions following completion of Phase III trials. Early review of detailed SAPs are also being requested by regulatory agencies; in some therapeutic areas requests for SAPs at End-of-Phase 2 meetings are becoming more common.

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A forthcoming Concept Paper to establish Points-To-Consider from the EMEA (the announcement can be found at <http://www.emea.eu.int/pdfs/human/ewp/245902en.pdf>) will be partially devoted to the topic of the appropriate role of statistical sections of protocols compared to SAPs, and the timing of SAPs. Quoting from the announcement:

“Blinded review of the data base (for e.g. the selection of a strategy to handle missing values) after the end of the observational period of phase III trials but before breaking the blind has become common in recent applications. During these blinded reviews often the statistical analysis plan is largely modified. At the same time more study protocols are submitted, where little or no information on statistical methods is provided and relevant decisions are deferred to a statistical analysis plan or even the blinded review. This attitude has not always had beneficial effects on the quality of clinical trials and has lead to regulatory concern.”

In the following articles, biopharmaceutical statisticians from two companies describe their experience creating analysis plans and evaluation of the content that has been both useful and required. As the articles demonstrate, there is variation in the internal consumers, and differences in approaches as regards to issues such as the inclusion of table shells, statistical computing instructions (e.g., SAS procedures), and plans for exploratory analyses.

The editors encourage readers with differing or additional experiences and relevant references to submit letters on the topic, and we will include as many of these as possible in a subsequent newsletter. Please correspond by email (see “Let’s hear from you”), and attach an MS Word file if possible.

#### References:

“Statistical principles for clinical trials”, ICH E9 *Harmonized Tripartite Guideline*.

“Concept paper on the development of a committee for proprietary medicinal products (CPMP) Points to Consider on methodological issues in confirmatory clinical trials with flexible design and analysis plan”, EMEA, 25 July 2002.

Armitage, P., and Colton, T. (1998), *Encyclopedia of Biostatistics*, New York: Wiley.

Kotz, S., Read, C., and Banks, D. (1999), *Encyclopedia of Statistics*, New York: Wiley.

Shein, C. (2000), *Encyclopedia of Biopharmaceutical Statistics*, New York: Wiley.

## Statistical Analysis Plan: Lilly Experiences

**Wei Shen, Timothy Costigan,  
Stacy Lindborg**

*Statistical Sciences, Eli Lilly and Company*

### Introduction

The statistical analysis methods associated with data collected from a clinical study are commonly documented at a high-level in the protocol. The statistical analysis section in the protocol often includes descriptions of the primary efficacy and safety analyses, and secondary analyses intended to support a label claim or commercialization efforts. However, the detailed methodology for secondary and exploratory analyses, as well as example tables and figures, are not presented in the protocol. Implementation of the statistical analysis methods as outlined in the protocol is a complicated task. Without a detailed plan for analysis, a delay can be experienced before results are available from a clinical trial. This delay in learning important clinical results can significantly impact the delivery of medicines to patients who are waiting for answers to their medical conditions. In addition, current ICH guidelines encourage a more technical and detailed elaboration of all pre-specified analyses. Therefore, a detailed analysis plan is necessary from both regulatory and practical perspectives.

At Eli Lilly and Company (Lilly), analysis plans have been developed by statisticians and used by the study team for several years. These analysis plans range from a detailed textual descriptions of the analyses needed for the clinical study report to a combination of textual descriptions and table shells. For a long time, the development of an statistical plan at Lilly was an informal process. However, recently, formal guidelines and processes on the analysis plan have been established. This paper describes the principles and processes underpinning the Lilly statistical analysis plan (SAP).

### Lilly Guidelines

The SAP is a stand-alone document, separate from the protocol. It contains full details about the statistical methodology and analyses for a clinical trial so that the planned analyses can be conducted in a consistent, repeatable manner. In addition, the SAP includes detailed parameters and data set information necessary for producing output reports as well as any plans for testing the robustness and sensitivity of the analyses. The SAP may also include example tables, figures, and listings (especially helpful when a third party will be responsible for analyses).

The purpose of the SAP is three-fold: 1) to document the plans for statistical analysis of clinical trial data prior to availability of unblinded data; 2) to gain alignment on the minimum scope of statistical analyses needed to support the clinical study report, registration, and/or commercial-

*(continued)*

ization needs for the compound; and 3) to ensure that sufficient resources are available to deliver on the statistical analyses in the specified timeframe.

A SAP is required for all clinical trials that are intended to support a label claim, with the exception of clinical pharmacology trials. However, a SAP is recommended for all clinical trials (including clinical pharmacology trials). It is recommended that a SAP be developed for all higher-level submission documents, particularly those that involve pooling of data from multiple studies, e.g., integrated summary of safety.

The development of the SAP encompasses various stages of a clinical trial. The SAP is an evolving document and is updated as the statistical analyses are further refined. Typically, two versions of the SAP are developed before the SAP is finalized. A preliminary version of the SAP contains written descriptions of the pre-defined primary and secondary analyses as well as a list of the planned analyses. Example output may be included. The preliminary SAP is completed as the protocol is developed and undergoes peer review with the protocol. A draft version of the SAP builds upon the preliminary SAP and incorporates detailed parameters for programming (data set requirements, variable derivations, and output report standards). The draft SAP is completed and approved around the time of first patient visit for the clinical trial. The final SAP consists of the final a priori detailed analysis plan for the clinical trial. The final SAP is approved prior to unblinding/data lock of the reporting database or the start of the study for open-label trials.

A SAP is prepared, reviewed, and approved by a cross-functional team, including statisticians, physicians, medical writers, system analysts, and regulatory scientists. The statistician, as the owner of the SAP, plays a major role in the development of the SAP. The main responsibilities of the statistician in the SAP development include: identification of appropriate statistical methods and analyses; approval of requirements for the reporting database, data set structure, and detailed parameters for programming output reports; assurance of process compliance; and approval of content. The potential users of the SAP include the study team, internal regulatory, marketing, and legal associates, as well as external reviewers.

As the SAP is developed, the statistical methods described in the SAP may differ from those described in the protocol. Any change to the primary analysis presented in the protocol or that affects a principal feature of the protocol design or study conduct requires a protocol amendment. Less significant changes to the statistical analysis methods described in the protocol may not require a protocol amendment. When deciding whether to amend a protocol based on changes to the SAP, the timing of other changes to the protocol, the regulatory environment, and ethical considerations should be considered. The decision to amend a protocol should be made in consultation with the regulatory scientist. If a protocol is amended for other reasons, any known changes to the analysis plan as presented in the protocol should be included in the protocol amendment.

## Lilly Experience with SAPs

Historically, style and content of SAPs varied across therapeutic areas and phases of research. In recent years, a template for the SAP was created for use by the Global Division of Statistical Sciences. The format of this template mimics the format of a clinical study report. The SAP captures all planned primary and secondary analyses, as well as anticipated exploratory analyses. The textual descriptions of the analysis methods are detailed and ready to implement. For example, an algorithm for site pooling, definition of subgroups, data transformation, adjustment of multiplicity, and structure of covariance matrices in the mixed effects models are fully described in the SAP. All report-ready shell tables are included and organized into appropriate sections of the SAP. These shell tables include complete descriptions of title, footnote, and report layout. In some cases, simulated data are used to generate the shell tables. Programming requirements necessary to generate these reports are included in the SAP, including data set requirements, variable derivations, specification of macro controls, and output report standards.

Besides the obvious benefits of having a SAP prior to database lock, the availability of a detailed SAP has enabled the process of a database lock and clinical study report preparation to become more efficient. The clinical trial reporting database can be built at the beginning of the study, and current data from the ongoing study can be transferred regularly. Reports can be generated based on these blinded data, and updated accordingly. By the time that the last patient visit occurs, programming for most of the pre-specified reports can be completed. Nearly all pre-specified reports can then be produced within days after database lock. As a result of a more detailed SAP, productivity and accuracy have been greatly improved. Cycle time from the last patient visit to database lock and from database lock to completion of clinical study report have been generally reduced, from a few months to about 30 days. The pressure for last minute requests for additions and changes has also been reduced. Of course, unanticipated analysis requests do arise after unblinding of the data. However, these requests are relatively small and can be completed quickly without delaying the completion of the clinical study report.

Regulatory guidelines, including ICH, were used to determine the content of statistical sections of protocols and the SAP. As previously indicated, one of the main drivers for a standardized SAP process was the current regulatory environment on pre-specification of the analysis plan. Pre-specification of the analysis plan lends credibility to the clinical trial results, which is particularly important for regulatory claims. The content of the SAP follows the ICH guidelines closely. For a typical study, the content includes: general considerations (e.g., significance level, site pooling); analysis data sets; subject disposition; subject characteristics; efficacy analyses; dose and exposures; safety analyses; subgroup analyses; and interim analyses. Discussions of adjustment of covariates, multiple comparisons and multiplicity, and handling of dropouts or missing data are also included.

*(continued)*

In some cases, regulatory agencies have requested an analysis plan, for example, at the pre-NDA meetings. The amount of information requested included an analysis plan for pivotal studies, an integrated analysis plan, and shell tables for primary and important secondary endpoints. Obtaining a priori agreement with the regulatory agencies on the analysis plan has helped to clarify expectations of upcoming analysis and avoid further regulatory questions.

The SAP provides a great benefit not only to statisticians, but also to a cross-functional team. The SAP brings a good opportunity for statisticians to provide a strong influence on data and analysis requirements. The system analysts contribute to the data set and report development, and can start their work early in the process. Medical writers, clinical research physicians, and regulatory scientists all have the opportunity to see a draft of the clinical study report, and can begin to draft the language for possible interpretation of the results even before the study is completed. A cross-functional collaboration on the SAP allowed elimination of redundancy and duplication of effort.

## Conclusion

A separate analysis plan is currently not required by all regulatory agencies. However, our limited experience has led us to realize the benefits of the SAP, in particular, for phase 3 clinical studies. The SAP is important to streamline statistical analyses needed to support registration and commercialization of our products. The use of the SAP has greatly improved the efficiency of database lock and clinical trial reporting process. As a result, cycle time from last patient visit to completion of study report has been reduced substantially, and accuracy and consistency of the statistical analyses have been improved. Synergies between statisticians and other functions have been achieved, and duplication of efforts has been avoided. The evolving versions of the SAP provide an audit trail to regulatory agencies on pre-specification of all analyses. A considerable amount of time is required to develop the SAP at the early stage of a clinical study; however, the benefit obtained at the end of the study is far greater. Starting with the "end in mind" is the key to the success of clinical development.

# Statistical Analysis Plans

**Stephen Eckert**

*Clinical Biostatistics, Ann Arbor Laboratories  
Pfizer Global Research and Development*

The purpose of a Statistical Analysis Plan (SAP) is to pre-specify the analyses that will be performed in order to interpret the data from a clinical trial. The SAP is written with primarily two audiences in mind: regulators and programmers. For regulators, the SAP provides proof that the sponsor's criteria for determining whether the drug is "effective" and "safe" were defined before the sponsor knew the results of the trial. For programmers (usually employed by, or under contract with, the sponsor), the SAP provides the basis for creating the statistical analyses and summaries for the trial data.

Why is pre-specification important? For the regulators, it provides some assurance that the sponsor didn't pick the most favorable analysis from a set of many possible analyses. Pre-specification is also necessary for the proper maintenance of false positive rates (Type I error rates) in the frequentist hypothesis-testing paradigm. For programmers, the pre-specification of analyses allows programs to be defined, created, and validated before completion of the trial, and thus, once the trial database is "locked" and the treatment codes unmasked, the statistical output can be generated very quickly.

It should be noted that statisticians have earned a reputation for being somewhat inflexible when it comes to analyses needing to be pre-specified. An old joke goes that pharmaceutical statisticians do not believe that Columbus discovered America, because his official plan stated that he was looking for the Spice Islands. Pre-specification of analyses is most important when alternate methods lead to different conclusions about the data. If every reasonable analysis that the sponsor and regulatory agency perform lead to the same conclusion, then the fact an analysis technique was not pre-specified shouldn't alter that conclusion. This idea of pre-specifying sufficient information in the SAP so that clear conclusions can be drawn is a good guide for determining its content.

So what should go in an SAP? To answer that question, we must first consider what was already written in the protocol, which is the document that governs the clinical trial. The primary audience for the protocol is the investigator (and perhaps also the Institutional Review Boards), as the protocol is the "instruction manual" for how to provide investigational therapy to trial subjects, and how to assure subject safety. As such, the following statistical items seem most appropriate to be included in the protocol (thinking from the investigator's point of view):

- **Endpoints.** How will we measure effectiveness and safety in an individual subject? Is change from baseline the important medical endpoint, or is percentage change from baseline? Oh yes, and which endpoints are "primary"? (More on primary vs secondary later in this article.)



**August 3 - 7, 2003**

**San Francisco  
JSM 2003**

San Francisco Hilton and Towers  
Renaissance Parc 55 Hotel  
Hotel Nikko San Francisco

<http://www.amstat.org/meetings/jsm/2003/>

• **Analysis sets.** We've spent considerable time and effort to enroll subjects in the trial and administer the therapy to them. Which, if any, will be excluded from analyses, and why will they be excluded?

• **Sample size.** After we spend the time and effort to enroll the trial, we want to be able to make valid conclusions. Are the assumptions that went into the sample size calculations reasonable?

• **Analysis timepoints.** My subjects have several choices for clinical trials. When will we get some understanding of whether the drug is working, so that we can best advise our patients on where to go?

• **Criteria for effectiveness and safety.** So, what will we conclude at the end of the day? Do we need to see  $p < 0.05$ ? If the trial is a non-inferiority trial, do we agree that a 10% decrease is non-inferior?

As the primary audience for the protocol is the clinical investigator, the amount of statistical detail in a protocol can vary. Some investigators take a keen interest in the statistical methodology, while some only want an overview.

So now we come to the content of the SAP. What should be included? The content of SAPs varies among sponsors, and will sometimes vary among different therapies within the same sponsor. But the following guiding principle makes writing the SAP easier:

The SAP should be written with enough statistical detail so that two independent statisticians who implement the SAP would come to the same conclusions, even if their outputs don't look the same.

A second principle that guides SAP writing is:

Any change to the SAP should require formal written approval from management, and all changes should be clearly denoted.

Using these guiding principles, the following paragraphs describe what information should be contained in the SAP, and what information can be relegated to other documents.

The first question that sponsors often face is "how much information from the protocol should we 'cut and paste' into the SAP?" The answer to this question is merely a matter of style, with reasonable arguments both for and against "cutting and pasting." The argument for just referring to the protocol is one that says "if the same information is presented in more than one place, it's very easy to make a copying mistake, or to forget to update the SAP when you update the protocol, and thus you create contradictions." The argument for cutting and pasting is that the primary audience for the SAP is different from the primary audience for the protocol, and thus the information should be copied to make the SAP more readable. I tend to agree with the latter argument, as I don't want to force the reader of the SAP to constantly flip back and forth. However, I do feel the other argument has merit. Thus, the SAP can either refer to the protocol, or cut and paste the following:

Background information that may be included for the SAP reader's information:

- Protocol title, phase, blinding status, randomized or not, single- or multi-center;
- Statement of trial design (e.g. parallel group);
- Sample size (with assumptions);
- Major entry criteria;
- Official study objectives.

Next, we turn to which items should be included in the SAP, because they will affect the interpretation of the trial data.

**Analysis Sets** (often called "populations" before ICH). Specific details should be provided on which patients should be included. As is recommended in ICH E9, the closer the analysis set is to the full randomized set, the more interpretable the analysis, and thus the reasons for excluding subjects from any analysis should be justified.

**Endpoint Calculations and Other Definitions.** How will you calculate your endpoints? What will you do if there is more than one baseline measurement? What if a subject is missing some or all of their assessments for a given endpoint? How much of an increase ALT is considered a safety issue? What will be considered the limit of non-inferiority? All of these questions need to be answered in detail. If two statisticians are to come to the same conclusions, the calculations of endpoint values for each subject, and the definitions of "clinical relevance," should be the same.

**Analysis techniques.** Analysis techniques for each endpoint should be spelled out in sufficient detail so that programmers can implement the analyses, and so that two statisticians implementing the analyses would come to the same conclusion. Statisticians should try to use their training to think of the "what if?" scenarios, and try to write instructions so that the programmers (and other statisticians) will know what to do if one of these situations arise.

**Rules for interpretation of analyses.** So, do you need  $p < 0.05$  for the trial to be successful? When will you use the phrase "statistically significant"? What about multiple endpoints, multiple time points, and interim analyses? What about the so-called "secondary endpoints?" (Note: In my opinion, there are two types of analyses: those where type I error is controlled [which I call "primary"], and those where type I error is not controlled [which I call "secondary"]. Some sponsors will describe both secondary and tertiary analyses; the difference is unclear to me.)

Now that we've described what should be included in an SAP, here are a few items that can be reasonably left out of an SAP. Keep in mind that changing the SAP should require formal (statistical) management approval.

**Detailed sample size assumptions.** Unless there is a plan to re-estimate sample size, or unless there is an official plan to assess the adequacy of assumptions, this detail is unnecessary, as it doesn't affect the conclusions. The final sample size is what it is. Besides, it should already have been specified in the protocol.

**Mock tables.** Details for how to produce the analyses are contained in the SAP. However, the layout of the tables,

content of titles, and content of footnotes are not relevant to the interpretation of the data—they are important for readability, but not crucial for scientific interpretation. Therefore, to keep the SAP to a reasonable length, it is acceptable to include mock tables in another document. (Also, changing the layout of tables need not require formal management approval.)

**Version of software to be used.** It is acceptable to mention that the latest available version of a software package will be used, but designating “All analyses will use PC SAS version 6.12” seems unnecessary, as receipt of updated software should not warrant an official amendment of the SAP.

**Description of the final dataset (variable names, etc).**

These items do not affect final interpretation, and so should be included elsewhere.

We have described the content of the ideal SAP. SAPs will of course have different look and feel across sponsors and drug programs. There are style and readability decisions that will vary among authors. However, by keeping to the two main principles of 1) providing sufficient detail so that two statisticians would come to the same conclusion, and 2) including only those items that would require formal approval if changed, a solid scientific SAP will meet the requirements of all audiences.

## Section News

### A Last Note from the Chair Bob Small

This is my last communication as chair of the Biopharmaceutical Section and I would like to spend most of the time thanking a number of people for their various efforts in support of the Section and me. We have one of the most active and accomplished Sections in the ASA. Some evidence for this is provided by the number of invited sessions we sponsor at the JSM each year, the joint sponsorship of several other meetings, the number of courses and Roundtables we put on at each JSM, and, of course, the size of our Section. This work takes a great deal of effort and is the result of a tremendous amount of work and cooperation. We would not be successful without the support of many members.

I hesitate to actually give recognition to the many who have made contributions this past year for fear I will forget the contributions of some. Undoubtedly I will because it is impossible to list all here. So I will apologize in advance to any that I slight and ask all to remember that still others have made significant contributions.

2001 ended with the postponement of our signature event, the Biopharm-FDA workshop because of the events of 9/11. My initial reaction was that we would cancel the event. But Greg Enas and Anna Nevius and their program committee pulled off a near miracle and rescheduled the meeting, got all of the speakers there, and managed a record attendance.

Len Oppenheimer put together great programs at both the ENAR and JSM meetings. On the whole it was the most



extensive showing at the meetings so far. Though it seems that Program Chair elect Stacy Lindborg has some very impressive programs coming for 2003. At the JSM the Section put on three courses that were very well attended. This substantial attendance was not only a measure of the service the Section provides to members, but also produced a profit in an otherwise difficult financial year. Joe Cappelleri had an excellent range of round tables at JSM that were also well attended.

The heavy burden of secretarial and treasury duties were taken care of by Kalyan Ghosh with a good deal of assistance from Amit Bhattacharyya. The Section has come to the conclusion that we really need to split the duties of Secretary and Treasurer. This year, on your ASA ballot, you will see a request to change the Section by-laws to produce this split. Thanks to Kalyan and Amit for managing an unmanageable situation.

Demissie Alemayehu took care of a variety of editorial and publication responsibilities, making deadlines and picking up when others drop the ball. Tuli Cnaan and Kay Larholt did yeoman's work keeping us in touch with the Council of Chapters and representing us well there. Nandita Biswas took care of the Section web page struggling against the laxity of others to keep it up to date and informative.

Sanat Sarkar and his student paper competition committee worked diligently to evaluate the entries and had to work against a revised deadline that made an already difficult task nearly impossible. Christie Clark took on the duties of chair of the Contributed Papers Competition Committee and lined up all of the support needed to get forms out and then collected and tabulated in a timely fashion. Sally Greenberg kept the mail list running for another year. Greg Enas, Bob Starbuck and Frank Rockhold formed the time consuming and difficult Fellows Committee.

I want to personally thank Jeff Meeker as past chair and Nancy Smith as Chair-elect for their support with several difficult issues this year. Their advice and help have been invaluable. Other Executive Committee members and sub committee members have been invaluable with their support advice and work. I can't thank them all individually but a heart felt thanks to all.

I mentioned that this had been a difficult financial year. We have been hit by a number of changes, some completely unexpected that have had a large negative effect on our finances. Among those have been the elimination of sales of proceedings, tremendous increases in expenses in Washington and New York, and the elimination of our Corporate Members program. The amount of money involved in these easily equals a year's worth of dues. We have taken steps to reduce expenses, and the income from the courses at JSM was very helpful. Also Len Oppenheimer has led an effort to begin a Corporate Sponsor program to replace the Corporate Members program we had.

The Section has been very successful over the past years due to the work of a large number of people and I am certain that it will continue to be as successful in the future given the professionalism, talent and enthusiasm of its members.

## Electronic Distribution of Biopharm Report

In keeping up the modern technology and to keep the cost down, *Biopharmaceutical Reports* will go ELECTRONIC from summer, 2003. Please update your email address with the ASA online directory. If you would like to receive the newsletter by postal mail, please respond to

Neal Thomas  
Pfizer, Clinical Biostatistics,  
50 Pequot Avenue  
New London, CT 06320  
Phone : 860-732-9942  
Email : [snthomas99@yahoo.com](mailto:snthomas99@yahoo.com)

Your cooperation in this respect will help the Section avoid any increase of the Section member dues for 2003.

## ENAR, Final Invited Program March 30 – April 2, 2003 Tampa, FL

### “Statistical Design and Analysis of Large High Throughput Screening Data for Drug Discovery”

Organizer/Chair: William J. Welch, University of Waterloo

### “Statistics in Genetics”

Organizer/Chair: Liwen Xi, Merck

### “Placebo-Controlled Trials: Ethics, Science and Economics”

Organizer: Stacy R. Lindborg, Eli Lilly / Frank Shen, Bristol-Myers Squibb

Chair: Frank Shen, BMS

### “Phase 2/3 Combination Designs to Accelerate Drug Development”

Organizer/Chair: Qing Liu, J&J PRD

## JSM, Biopharm Final Invited Program August 3 – 7, 2003 San Francisco, CA

### Joint Session Biopharm/Bayesian Section: “Bayesian Methods in Medical Device Clinical Trials”

Organizer: Stacy R. Lindborg, Eli Lilly

Chair: Brad Carlin, University of Minnesota, Biostatistics

### “Bridging Data Between Two Ethnic Populations: Statistical and Regulatory Implications”

Organizer/Chair: Prof. Byron Jones, GlaxoSmithKline Pharmaceuticals

### “Multiple Comparison Issues in Clinical and Pre-clinical Trials”

Organizer/Chair: Sanjib Basu, Division of Statistics, Northern Illinois University

### “Use of Robust Methods in Clinical Trials”

Organizer/Chair: Ji Zhang, Ph.D., Sr. Director, Clinical Biostatistics, Merck Research Laboratories

### “Choice of the Primary Analytical Method for Longitudinal Clinical Trials With Subject Dropout”

Organizer: Walter W. Offen & Craig Mallinckrodt, Eli Lilly

Chair: Walter W. Offen, Eli Lilly

### “Reverse Multiplicity in Two Co-primary Endpoint Comparisons”

Organizer/Chair: Y. Fred Yang, Ph.D., Global statistics and programming, Pharmacia

**THE 26th ANNUAL MIDWEST BIOPHARMACEUTICAL  
STATISTICS WORKSHOP  
MAY 19—21, 2003 • BALL STATE UNIVERSITY, MUNCIE, INDIANA  
Preliminary Program**

**MONDAY, MAY 19  
8:30 am–5:00 pm**

**WORKSHOP REGISTRATION**

FEE: \$145 until May 1 (\$50 for students)  
\$165 after May 1

**9:00 am–1:00 pm  
SHORT COURSE**

**(Separate Registration Fee: \$55)**

Presenters: NAGARAJ NEERCHAL, University of  
Maryland Baltimore County, and JORGE MOREL,  
Procter & Gamble

Topic: Analysis of Categorical Data with Overdispersion  
(Extravariation)

**2:15 pm–2:30 pm**

**INTRODUCTION AND WELCOME  
CYRUS HOSEYNI, Pfizer**

**2:30 pm–4:30 pm  
PLENARY SESSION**

Speaker: MURRAY CLAYTON, University of  
Wisconsin, Madison

Topic: The Art of Statistical Consulting

**TUESDAY MORNING, MAY 20  
CONCURRENT SESSIONS  
8:30 am—11:15 am**

**A. Risk Management: When the Label is  
Not Enough**

*Organizer/Chair: Brenda Crowe, Eli Lilly*

“Risk Management—An Overview,”  
David Hyslop, Eli Lilly

Topic and speaker to be announced

Topic and speaker to be announced

**B. Analysis of Large Datasets in Preclinical  
and Early Development**

*Organizer/Chair: Stan Young, National Institute of  
Statistical Sciences*

“Analysis of Chemistry Data,” Andy Liaw, Merck

“An overview of Support Vector Machines and  
Kernel Methods,” J. Stephen Marron, University  
of North Carolina

“Linear Methods in Classification and Prediction,”  
Kerry Bemis, Eli Lilly

**C. Statistical Issues Related to Develop-  
ment, Manufacture, and Control of  
Biotech Products**

*Organizer/Chair: Robert Dillard, Pharmacia*

“Design Issues in Bioassay with Emphasis on the  
Split Plot Nature of Typical Designs,”  
David Lansky, Lansky Consulting

“Modeling Issues in Bioassay with Emphasis on  
Nonlinear Approaches and Similarity Testing,”  
Stan Altan, PRDUS, Johnson & Johnson

“Specifications and Monitoring of Biotech  
Products with Emphasis on Making Stability and  
Specifications Come Together,” Robert Capen,  
Merck

Discussant: Tim Schofield, Merck

**TUESDAY AFTERNOON, MAY 20  
POSTER SESSION  
12:00 pm–1:30 pm**

Chair: Jackie Reisner, Pharmacia

Posters will be accepted on any  
biopharmaceutical statistical topic.

Abstracts must be received by May 1.

Students may qualify for the Charlie Sampson poster  
award if abstract received by April 1.

**For more information contact  
Jackie at (616) 833-8332 or  
jacqueline.k.reisner@pharmacia.com**

**TUESDAY AFTERNOON, MAY 21  
CONCURRENT SESSIONS  
1:30 pm–4:15 pm**

**A. Novel Approaches for Analyzing Clinical  
Safety/Adverse Event Data**

*Organizer/Chair: Devan Mehrotra, Merck*

“Nonlinear Mixed Effects Modeling of Adverse  
Event Severity Scores,” Ken Kowalski and Lynn  
McFadyen, Pfizer

“Multiplicity Considerations in Evaluating Safety  
in Clinical Trials,” Joe Heyse and Devan Mehrotra,  
Merck

“Sequential Procedures for Monitoring Adverse Events,” Vladimir Dragalin and Valerie Fedorov, GlaxoSmithKline

Discussant: Janet Wittes, Statistics Collaborative

## **B. Tools and Techniques for Analyzing Large Data Sets**

*Organizer/Chair: Kjell Johnson, Pfizer*

“Efficient Algorithms for Statistical Mining of Very Large Life Sciences Data Sets,” Andrew Moore, Carnegie Mellon University

“Interpretable Dimension Reduction in Drug Discovery,” Hong Gu

“High Dimensional Visualizations,” Georges Grinstein

## **C. Preclinical Safety Assessment**

*Organizer/Chair: Lori Mixson, Merck*

“Analysis of in vivo Models for Safety Pharmacology Studies—ICH S7 Guidelines and Best Science,”  
Speaker to be announced

“Statistical analysis of rodent carcinogenicity studies—Peto vs. poly-K trend analyses,”  
Speaker to be announced

“Incorporating historical control data into the analysis of carcinogenicity studies,”  
Speaker to be announced

“Maximizing power and assessing the false-positive rate in rodent carcinogenicity studies,”  
Speaker to be announced

## **TUESDAY EVENING BANQUET Announcement of Student Winner of Charlie Sampson Poster Award Speaker: To be announced**

## **WEDNESDAY MORNING, MAY 21 CONCURRENT SESSIONS 8:30 am–11:15 am**

### **A. Analysis of QT/QTc Interval Data**

*Organizer/Chair: Marilyn Agin, Pfizer*

“Electrocardiogram Reference Ranges for Lilly Clinical Trials,” Alexei Dmitrienko, Eli Lilly

“Covariate-Adjusted Analysis of QT Interval: Population and Individualized Corrections,” Brian Smith, Alexei Dmitrienko, Eli Lilly

“Individual and Population Correction of QT Data,”  
B. Nhi Nguyen, U.S. Food & Drug Administration

“Electrocardiographic Identification of Drug-Induced QT Prolongation: Assessment by Different Recording and Measurement Methods,” Steven F. Francom, Pharmacia

“Assessing QT Variability in Healthy Volunteers,” Robert Abel and Daniel Strieter, Pfizer

### **B. Analysis of Large Data Sets in Clinical, Regulatory and Marketing**

*Organizer/Chair: Bob Small, GlaxoSmithKline*

Topics and speakers to be announced

### **C. Current Issues in Stability**

*Organizer/Chair: William Myers, Procter & Gamble Pharmaceuticals*

“Stability Monitoring in a Multi-lot Environment,” William Fairweather, Flower Valley Consulting

“Mitigating Risk Through Proper Interpretation of Annual Stability Study Data,” Tim Schofield, Merck

“Shelf Life Determination—The ANCOVA Approach,” Yi Tsong, U.S. Food & Drug Administration—CDER

FOR MORE INFORMATION ON THE WORKSHOP, please contact MIR ALI, Ball State University, (765) 285-8670, Email: [mali@bsu.edu](mailto:mali@bsu.edu) or YING ZHANG, Quintiles, (816) 767-4679, Email: [yings.zhang@quintiles.com](mailto:yings.zhang@quintiles.com). The preliminary program will be updated periodically at the web site <http://www.mbswonline.com/>

# Meeting Minutes Biopharmaceutical Section Executive Committee

## Transition Meeting

Thursday, Dec. 12, 2002

## ASA Headquarters

**Attendees:** Bob Small (GSK), Amit Bhattacharyya (GSK), Keith Soper (Merck), Len Oppenheimer (Merck), Jeff Meeker (BMS), Margaret Minkwitz (AstraZeneca), Nancy Smith (FDA), Kalyan Ghosh (Merck).

### Approval of Minutes of August Meeting

Ghosh / Bhattacharyya

Minutes Approved :

### Budget Issues

Ghosh / Bhattacharyya

### Discussions :

The 'cash in hand' is satisfactory, thanks to profit from the continuing education courses at the 2002 JSM.

Proposal was made that the ASA needs to include the proceedings in the JSM registration to get to make it easier to buy the proceedings.

Bob Small to contact Corsi and Wasima for the final budget for the 2003 FDA/Industry Conference

Budget tentatively accepted contingent upon agreement on the FDA conference budget.

**Assignment: Bob will set up a teleconference involving Rida, Small, Ghosh and Sanders to discuss the budget.**

### Corporate Sponsorship

Oppenheimer

### Discussions :

"Solicitation letter" and "corporate sponsor response form" drafted and sent for review. To be revised with guidance from ASA (Steve Porzio) so that this is seen as a contribution and not 'advertisement'.

Sponsors' list can be displayed in any Biopharm sponsored event. Sponsor's Logo (if available) and a link to their web site can be displayed as well.

Routing of Contributions discussed and accepted through Biopharm Section Treasurer and ASA (Steve Porzio). Kalyan will be sent a copy of the checks, and subsequently Len Oppenheimer will be informed monthly of the Sponsors' contribution for keeping an up-to-date list of the contributors.

Timeline: The mailing of the letter will be in January and follow-up phone calls by March 2003.

The Executive committee acknowledges and appreciates the significant work Len Oppenheimer has done in this initiative.

**Motion:** Philadelphia Chapter of ASA had requested \$1000 donation from the Biopharm section for organizing a series titled "A Sesquicentennial of Statistics". The executive committee rejected this request at this time.

### 2003 Programs

Lindborg

Stacey L has organized an impressive list of invited sessions for the ENAR and JSM 2003. The Executive Committee thanked her for a job well done.

### Charter Amendment

Meeker

### Discussions:

The amendments have now been rewritten in the new format required by ASA.

The amendments accepted at the last meeting needs to be voted by the membership. This would be in the 2003 ballot.

Bob to work with Nandita Biswas to put this on the web site.

A column with this announcement would be in the *Amstat News*.

### 2003 Committee Appointments

Marsh

### Discussions :

Mani S. (Centocor) has accepted a Board appointment. Nancy has offered another position and is waiting for acceptance.

Need to fill up 2 members in the "Fellow Committees". The members have to be ASA fellows themselves. Few names have been mentioned to Nancy M. who will make contacts as appropriate.

Nancy M. will be working on other appointments in a few other committees.

**Assignment: Publication manager to contact Muncie Mtg. Liason for inclusion into the ASA proceedings.**

### Other Business/Summary Actions

All

Founder's Award: The committee discussed the possibility of finding someone for this award. Criteria includes (i) Long term commitment to ASA in at least 3 major areas and (ii) made some contribution which lasts more than the person's term in the office.

This was Jeff Meeker's last attendance at the executive team meetings since he is retiring soon. The Executive Committee acknowledges and thanks Jeff for his significant contribution to the Biopharm section and the ASA over several years. His colleagues at the Executive Team will certainly miss him.

### Meeting Adjourned



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 Shipping of JSM 2001 Proceedings will take about 2-3 weeks.  
 2002 Proceedings CD-ROM will begin shipping in February 2003.

## Let's Hear from You!

If you have any comments or contributions, contact Editor Neal Thomas, Pfizer, Clinical Biostatistics, 50 Pequot Avenue, New London, CT 06320; Phone 860-732-9942; email: [snthomas99@yahoo.com](mailto:snthomas99@yahoo.com), Associate Editor Kevin W. Anderson, [kwanderson@rcn.com](mailto:kwanderson@rcn.com); or Past Editor Kannan Natarajan, Director, Biostatistics, Bristol-Myers Squibb PRI, P.O. Box 5400, Princeton, NJ 08543; Phone 609-818-4299; email: [kannan.natarajan@bms.com](mailto:kannan.natarajan@bms.com).

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