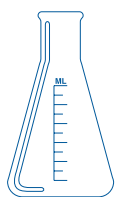


## Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

Volume 11, No. 1

Spring 2003

Chair: *Bob D. Small*

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

## Electronic Distribution of Biopharmaceutical 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. There will be one report with both electronic and paper formats. Email notification of new reports will be sent to members with the web address where the report can be accessed. Large attachments will not be sent. Your cooperation in this respect will help the Section avoid any increase of the Section member dues for 2003.

## Letter from the Chair

Nancy D. Smith

2002 was a very productive year for the Biopharmaceutical Section, and we are well on the way toward having a record year in 2003. We hope you will spend a little time looking through this issue to acquaint yourself with everything that is going on in the Biopharmaceutical Section. I think you will be proud that you are a part of the largest and one of the most active Sections in the American Statistical Association. Keith Soper wrote a great article for the Biopharmaceutical Section column in *Amstat News* in December that we are reprinting here. The cost of Section membership is small, but the benefits to the biostatistical community are very large.

We had a very productive spring Board Meeting at the ENAR with 18 Members in attendance. I want to offer my congratulations to the new elected members of the Board. Keith Soper of Merck is the new Chair-Elect, Anna Nevius of the FDA was elected Program Chair, and Katherine Monti of Rho, Inc. is the new Representative to the Council of Sections.

*(continued)*

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If you are coming to the Joint Statistical Meetings (JSM) in August, please plan to join us for the Biopharmaceutical Section Business meeting on Tuesday evening from 5:00 to 6:30 p.m. This is a great opportunity to network with your fellow statisticians from industry, regulatory agencies, contract research organizations, and academia. Everyone is encouraged to attend the meeting and become more active in section activities.



The Biopharmaceutical Section web site has recently been updated, and new items are being added on a regular basis. Please check out the folks who represent you on the board and let us know if you would like to get involved on any of the committees or other groups. If you are interested in running for an elected office, please contact

Bob Small. He will be putting together the list of nominations for 2005 officers during June and July.

The Biopharmaceutical Section continues to expand with new activities and more benefits for members. We had six strong sessions at the recent ENAR meeting in Tampa, with standing room only in several cases. We will also have a very visible presence at the Joint Statistical Meetings in San Francisco in August. Elsewhere in this issue you can learn about our invited sessions and special contributed sessions that cover a broad range of interest areas, and promise to be very interesting. Stacy Lindborg has done a truly outstanding job as Program Chair, organizing and coordinating all of the sessions. We also have fourteen luncheon roundtables at the JSM, and hope everyone will check the list and plan to participate in at least one roundtable. Anna Nevius is getting a head start on next year's role as Program Chair by coordinating the roundtables for the 2003 JSM. It may seem like a long time from now, but this is the time to think about submitting session ideas for the 2004 ENAR meeting in Pittsburgh and the JSM meeting in Toronto. In fact, the deadline for submissions is early June. Please see the note from Anna in this issue and respond promptly if you are interested in developing a session for JSM or ENAR.

Corsee Sanders of Genentech Inc., and Wasima Rida of the FDA have done a great job planning the FDA/Industry Statistical Workshop scheduled for September 18–19 at the Hyatt Regency in Bethesda, Maryland. An announcement for the conference containing a web address for the preliminary agenda and registration forms for the meeting are included in this issue. Because Wasima is leaving the FDA in May, Ed Nevius will be joining Corsee and Wasima as a third chair for the meeting.

Len Oppenheimer and the Corporate Sponsorship committee have designed a Sponsorship program that should benefit the Biopharmaceutical Section for many years. As of last week, we already have 16 Corporate Sponsors! We will be listing the sponsors in this newsletter and *Amstat News*, and have a poster listing them at our Business Meeting at the JSM and at the FDA/Industry Workshop. Many thanks to Len and his committee for their work developing this outstanding program!

See you in San Francisco!

Nancy

## Member Benefits

Keith Soper

The Biopharmaceutical Section is one of the largest and most active Sections in ASA. Being a member directly benefits you and strengthens the statistical profession both in the pharmaceutical industry and in the agencies that regulate them. If you are already a member, take a moment to review the benefits and consider the opportunities to get more involved. If you are not a member, read on! You'll be amazed at what you get for the \$8 annual dues, or \$1 for students.

Included in the dues is our newsletter the "*Biopharmaceutical Report*" which has practical articles for statisticians in our industry, such as *Adaptive Trials and Bayesian Statistics in Drug Development*, by Don Berry. The newsletter is only one of the ways our Section works to facilitate communication among statisticians.

Another is our annual FDA/Industry workshop, which enables regulatory, and industry statisticians to discuss scientific and process issues central to drug development without focusing on a particular submission. The workshop is always well attended by both industry and regulatory statisticians, with many sessions co-chaired by a statistician from each arena. If you would like to see an in-depth discussion of any statistical topic from both points of view, let us know, or even consider organizing a session. The next meeting will be in the Washington D.C. area in September 2003.

Have a smaller question, perhaps about the study design on your desk and not sure who may have experience with it? Post your question on our electronic mailing list and start a discussion with other Section members around the country. Want a longer discussion face to face? Drop in on one of our luncheon roundtables at the Joint Statistical Meetings (JSM). The Section sponsors around ten roundtable discussions each year, and is always looking for good subjects (and discussion leaders).

Like all Sections, we help to organize invited and contributed sessions at JSM each year. We also help organize sessions at the ENAR meeting. Our goal is to provide topics relevant to your work that stimulate your thinking, keep you up with the latest developments and help you deliver the highest quality product. Most JSM and ENAR meetings have short courses sponsored by the Biopharm Section as well.

The Section also seeks to promote and recognize excellence in our profession. If you are a student in our Section, consider submitting your paper to our judges for Best Student Paper. We often give several cash awards. If you are a professional in our section, you may win an award for Best Presentation of a Biopharmaceutical Contributed Paper. If you want to honor a colleague, submit their name to our Fellows Committee, which can help leaders in our profession gain recognition as ASA fellow.

Behind the scenes, your executive committee does many things to help coordinate conferences outside the ASA. We have liaisons with the ASQ (Deming) and MidWest Biopharmaceutical (Muncie) conferences.

Just want to network with other pharmaceutical industry statisticians while at JSM? Come to our annual business meeting, always efficiently short on business and long on social connections. We look forward to seeing you in San Francisco this summer!

## Joint Statistics Meeting 2003

### Biopharm Final Invited Program

Joint Session Biopharm/Bayesian Session **“Bayesian Methods in Medical Device Clinical Trials”** Organizer: Stacy 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, PhD, Sr. Director, Clinical Biostatistics, Merck Research Laboratories

**“Choice of the Primary Analytical Method for Longitudinal Clinical Trials w/ Subject Dropout”** Organizer: Walter W. Offen & Craig Mallinckrodt, Eli Lilly Chair: Walter W. Offen, Senior Research Scientist, Eli Lilly and Company, Lilly Corporate Center

**“Reverse Multiplicity in Two Co-primary Endpoint Comparisons”** Organizer/Chair: Y. Fred Yang, PhD, Global statistics and programming, Pharmacia

### Biopharm Topic Contributed Sessions

*Statistics Applications in the Omics Area in the Biopharmaceutical Industry*

*Statistical Issues with Therapeutic Medical Devices*

*Statistical Issues with Diagnostic Medical Devices*

### Biopharmaceutical Roundtable Luncheons JSM 2003

Peter A. Lachenbruch—Division of Biostatistics/ OBE/ CBER

**Title:** Vaccine Lot Consistency Issues

Stephen Wilson—FDA

**Title:** Electronic Submissions, Data Standards, Data Warehouses and Analysis Databases

Berton H. Gunter—Merck & Co.

**Title:** Statistics and Scientific Practice: Shall the Twain Ever Meet?

Qing Liu—The RWJ Pharmaceutical Research

**Title:** Regulatory, Ethical and Statistical Issues of the FDA's Accelerated Approve Process

Sue-Jane Wang—CDER/FDA

**Title:** Pharmacogenomics/pharmacogenetics studies in drug review

Qi Jiang—Merck Research Laboratory

**Title:** Sample Size Calculation for Survival Studies

Thomas J. Permutt—FDA

**Title:** Adjustment for Covariates in Randomized Clinical Trials: A Regulator's Perspective

Devan V. Mehrotra—Merck Research Laboratories

**Title:** Stratified Clinical Trials—Some Food for Thought

Jimmy Thomas Eford—Stanford School of Medicine

**Title:** Standard Operating Procedures (SOPs) From a Statistician's Perspective

Hsien-Ming James Hung—FDA

**Title:** Non-inferiority Active Control Trial

Charles F. Contant, Jr.—Baylor College of Medicine

**Title:** The Role of Statisticians and Statistical Review in the Institutional Review Board

Thomas P. Capizzi—Merck Research Laboratories

**Title:** Impact of Secondary Endpoint Multiplicity Issues on Drug Development Programs

Amit Bhattacharyya—SmithKline Beecham

**Title:** Trend Test in pharmaceuticals, How prevalent should it be?

Gregory Campbell—FDA

**Title:** Statistical Issues in Medical Device Studies

### Short Courses

*The Biopharm Section is sponsoring two strong Short Courses for JSM 2003—be sure and register early! Spaces will go quickly.*

**Design and Analysis of Cross-over Trials**, taught by Professors Byron Jones and Michael G. Kenward.

*Abstract:* The course will provide a thorough introduction to the statistical design and analysis of cross-over trials and will be illustrated throughout with numerous examples taken from real pharmaceutical and other trials. Examples of code to undertake analyses using the SAS<sup>®</sup> statistical analysis system will be given.

The topics to be covered include: The 2 x 2 trial—analysis of continuous, binary and categorical data, nonparametric and Bayesian analyses, preliminary testing for carry-over. Designs for two treatments with more than two periods or sequences. Designs for three or more treatments. Analysis of continuous and categorical data for general cross-over trials. Bioequivalence testing.

**Exploration and Analysis of DNA Microarray Data**, taught by Drs. Dhammika Amaratunga and Javier Cabrera.

*Abstract:* We offer a comprehensive course covering the process of analyzing DNA microarray data from A to Z.

A typical analysis involves a preprocessing stage and a processing stage. In the preprocessing stage, microarrays are checked for quality, systematic effects are removed by nonlinear normalization and data are screened for outliers and other unusual features. At the processing stage, the preprocessed data are analyzed to pick up gene expression patterns that differ significantly across the different cell types. This can be done using a gene-by-gene approach with conventional statistical methods or with more sophisticated tools that incorporate strategies for pooling information across genes, either through modeling, Bayesian-type arguments or supervised clustering.

In this short course, we intend to cover many of the statistical considerations involved in a typical microarray data analysis. We will do this mainly in the context of a single microarray dataset, through which we will illustrate the statistical issues involved at both stages of the analysis and many of the more promising statistical approaches. A software package (DNAMR) implementing the DNA microarray analysis methodology will be provided.

## Call for Invited Sessions in 2004

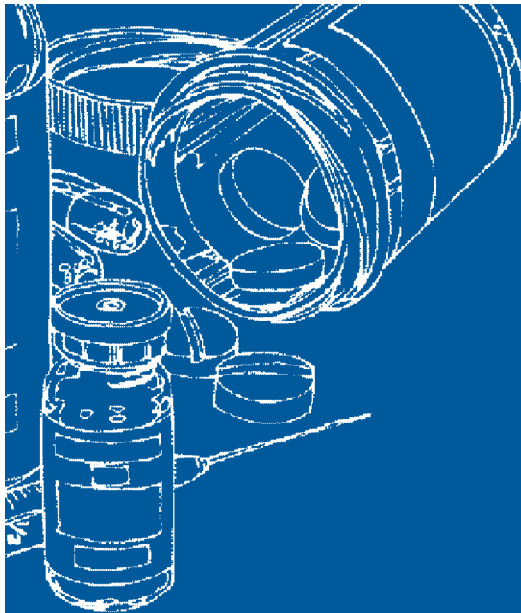
### Anna Nevius

As Program Chair for 2004, I am looking for ideas for invited paper sessions for both the 2004 ENAR Spring meeting and 2004 JSM. The deadline for ENAR is June 1 and the deadline for JSM is June 15. 2004 ENAR is in Pittsburgh, Pennsylvania, March 28–31, 2004 and 2004 JSM is in Toronto, Canada, August 8–12, 2004. We will put our proposals in a competition pool so the more detailed the ideas for the sessions are, the better chance that we have of getting the sessions accepted.

The proposed theme for the 2004 ENAR Spring meeting is “Expanding the Focus of Biometrics”. The committee is looking for ideas for invited paper sessions. One specific topic for an invited session topic that has been suggested is methodology for analyzing adverse events in clinical trials. I am also looking for other ideas for sessions to enter into the competition.

I am also looking for ideas for JSM on topics that we think would be of interest to our Section members and to the entire Association. Sessions on hot topics in statistics with well-known statisticians and lots of detail will give an advantage to a proposed session.

If you have any questions, please email or call: Anna Nevius 301-827-0218. ANEVIOUS@CVM.FDA.GOV



## FDA INDUSTRY WORKSHOP

Register ONLINE at  
[www.amstat.org/  
meetings/fdaworkshop](http://www.amstat.org/meetings/fdaworkshop)

## FDA/Industry Workshop

Corsee Sanders, Wasima Rida, and Ed Nevius

The 2003 FDA/Industry Workshop will be held September 18–19 at the Hyatt Regency in Bethesda, Maryland. There will also be two short courses offered the afternoon of September 17. Sponsored by the FDA Statistical Association and the ASA Biopharmaceutical Section, this meeting offers a chance to exchange views with a broad range of people from regulatory agencies, the pharmaceutical and biotech industry, academia, and others interested in drug, biologics, and medical device development.

The theme for this year's workshop is “Statistics: From Theory to Regulatory Acceptance.” The first day offers four plenary sessions on flexible trial designs, longitudinal data analysis, clinical trial monitoring, and perspectives on safety issues in drug development. The second day is composed of three parallel sessions. For the first parallel session, attendees can choose from discussions on time-to-event data, issues with multinational trials, and genomics in drug discovering and development. Topics to choose from the second parallel session are analysis database (AdAM), post-marketing issues, and using information from preclinical and early clinical studies. The third parallel session offers discussions on randomization, diagnostics, and getting the dose right in Phase I and II trials.

At the end of the second day, there will be three (parallel) special interest sessions. Those sessions discuss medical devices, surrogate endpoints in vaccine trials, and statistical methods in advisory panel meetings.

Two short courses are offered on the afternoon of September 17 for an additional fee of \$55. Ron Helms from Rho, Inc., will teach a course on handling missing data in longitudinal studies. George Chi and Gang Chen from FDA will organize a course on active control non-inferiority trials.

Registration will open in early May. Please see the ASA web site <http://www.amstat.org/meetings/fdaworkshop> for the registration form, preliminary program, and list of workshop organizers. On behalf of the organizing committee, we look forward to seeing you in September.

# Corporate Sponsors Program 2003

The Biopharmaceutical Section has implemented a Corporate Sponsors Program to allow the section to maintain and enhance our many activities without being forced to continually increase section dues. Some of the many efforts that the section supports include the following:

i.) Annual FDA/Industry Workshop (co-sponsored with the FDA) which attracts experts from the pharmaceutical industry, FDA, and academia to exchange ideas in both formal presentations and in informal conversations during breaks, lunch, etc. The next workshop will occur September 18-19, 2003 in Bethesda, Maryland.

ii.) The Section publishes (2-3 times a year) a newsletter called the "*Biopharmaceutical Report*" which has practical articles for statisticians involved with biopharmaceutical applications, such as "*Adaptive Trials with Bayesian Statistics in Drug Development*" by Don Berry.

iii.) Like all ASA Sections we help to organize invited and contributed sessions, roundtable luncheons at both the ENAR Spring Meeting and the summer JSM meeting. We focus on topics/areas that are relevant to section members, stimulate their thinking, keep them up to date with the latest developments, and promote excellence in biopharmaceutical statistical practice. Most ENAR and JSM meetings have short courses sponsored by the section.

iv.) The Section also seeks to promote and recognize scientific/research excellence. For students, we provide Best Student Paper cash awards. For senior professionals, we offer awards for Best Presentation of a Biopharmaceutical Contributed Paper.

v.) Behind the scenes, the Section executive committee helps to coordinate with conferences outside the ASA via liaisons with ASQ (Deming Conference in December) and the MidWest Biopharmaceutical (Muncie) meetings.

Through the efforts of the Corporate Sponsors Committee,

**Len Oppenheimer**—Merck Research Labs (Chair)

**Kay Larholt**—Genzyme, Inc.

**Brian Wiens**—Amgen

**Russ Helms**—Rho, Inc.

The following companies have generously agreed to participate:

Allergen	Genzyme	Purdue Pharma
Amgen	GlaxoSmithKline	Sanofi-Synthelabo
Astra Zeneca	Johnson & Johnson	Schering-Plough
Aventis	Merck	Wyeth
Bristol-Myers Squibb	Novartis	3M Pharmaceuticals
Centocor	Pfizer	

We will recognize our current and future sponsors in all our official venues including section publications, the section web sites, and at scientific meetings where we have an active presence.

If your company is not listed above and would like to become a Corporate Sponsor, please have the following form completed along with a \$500-\$1500 contribution (\$1000 recommended) payable to the American Statistical Association. The ASA is a 501(c) (3) non-profit organization and, as such, contributions are tax deductible.

Mail to:

Biopharmaceutical Section Corporate Sponsorship  
 American Statistical Association  
 1429 Duke Street  
 Alexandria, Virginia 22314

Please note "BIOPHARMACEUTICAL CORPORATE SPONSOR" on the check.

If you require more information, contact Len Oppenheimer at [leonard\\_oppenheimer@merck.com](mailto:leonard_oppenheimer@merck.com).

### Biopharmaceutical Section Corporate Sponsorship Form 2003

To become a Corporate Sponsor of the Biopharmaceutical Section for 2003:

Make a \$500-\$1500 (\$1,000 recommended) contribution, payable to the American Statistical Association

Complete the information below.

Send the form to: **Biopharmaceutical Section Corporate Sponsorship**  
 American Statistical Association, 1429 Duke Street, Alexandria, VA 22314-3415

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*Person to whom future mailings should be sent.*

Phone Number: \_\_\_\_\_ E-Mail Address: \_\_\_\_\_

If you'd like your Corporate web site address & logo to be included on the Biopharmaceutical Section web site, please provide:

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## Letters

### Statistical Analysis Plans

Andrew J. Dunning

*Wyeth Vaccines Research*

Stephen Eckert raises a number of interesting questions in his article about Statistical Analysis Plans (SAPs). Though I would not disagree with almost anything he says, here are a few alternative answers.

The article sets out a number of principles that SAPs might follow. As a single guiding principle, the purpose of the SAP may be stated as:

The Statistical Analysis Plan sets out how the questions posed by the study objectives are to be answered by the data collected.

This incorporates the element of pre-specification which Eckert uses as his starting point, but it also leads to answers to some of the other questions he raises.

The study objectives guide the endpoints and methods selected in the analysis plan. Presumably the study was designed to answer the questions posed by the objectives, and the data collected was intended to provide the answers. The SAP provides the bridge between the two. There may be other scientifically interesting questions that the data could provide answers to, and these can be addressed in exploratory analyses, but they are unlikely to lead to product approval without further studies. The principle function of the analysis is to answer the questions posed by the objectives.

Both Eckert and Shen et al. raise the question, Who is the target audience of the SAP? Who is it written for? and suggest that the target audiences are both the regulatory agencies who will review the submission and the programmer who will write the SAS code. However, the interests of these two audiences are frequently at odds. The member of the FDA Advisory Committee would like to quickly find the description of the statistical methods used to answer the primary objectives, from among the boxes of materials they receive for each submission. They probably have little interest in the detailed instructions to the SAS programmer; however, these cannot be ignored. At some point, decisions must be made such as whether the illness episode is to be considered to have occurred on the reported illness onset date or the date the subject was seen by the physician, and for reproducibility these must be pre-specified.

Thus the SAP is faced with the dual task of clearly setting out the methods used to evaluate the primary endpoints of the study, while at the same time specifying the detailed conventions needed by the programmer. Does this lead us to two documents—one setting out the statistical methods used to evaluate the principle study objectives and another specifying the details? Eckert suggests that the mock tables could be included in “another document”; this might also be a place for the details of the data manipulation and coding algorithms and conventions, thus freeing the analysis plan to address statistical methods rather than data conventions. and sparing the advisory committee member from having to wade through the latter, unless he really wanted to.

The guiding principle given above also suggests an answer to the ‘cut and paste’ question raised by Eckert, How much information from the protocol should we cut and paste into the SAP? If the Statistical Analysis Plan sets out how the questions posed by the study objectives are to be answered by the data collected, it should reiterate the objectives. Then, in describing the design and conduct of the trial, it should do so in a way that focuses on how the data was generated and collected. Technical and clinical details of the trial design—the conduct of study visits and the methods used for assays—can be left to the protocol. But summarizing the data collection procedures, together with the objectives, sets out a framework for the statistical methods to provide the link from the one to the other.

For example, the reader of the SAP does not need to know the detailed instructions—many relating to patient safety and consent—set out in the protocol and the case report form instructions for the conduct of each patient visit, but it is helpful to know that patients were examined, say 3, 7, 14 and 21 days after the start of treatment, for fever and adverse reactions.

*(I am a Principal Statistician with Wyeth Vaccines Research, though needless to say the opinions in the letter are mine alone and not those of my employer.)—Andrew J. Dunning*

### Why Statistical Analysis Plans Should Not be Created Before Unblinding Data

David Salsburg

*Pfizer*

The Winter, 2002, issue of *Biopharmaceutical Report* was devoted to examination of the development of Statistical Analysis Plans (SAPs) in preparation of NDAs. Shen, Costigan, and Lindborg [3] and Eckert [2] point out that it is very useful to prepare for the statistical analysis of clinical data long before data are available and to adjust it to the realities of data as they are observed in the unblinded developing data files. This is because the hardest, and most time consuming, part of statistical analysis is the organization of SAS files and the structures of report tables and graphs, and a great deal of that work can be done without ever looking at a comparison of treatment groups. Thus, I applaud the development of such careful preparation.

However, I think that the reason given by regulatory authorities for SAPs is mathematically invalid and, if followed blindly, can lead to the inappropriate use of statistical hypothesis tests in the analysis of clinical data. In the Forward to the two papers [1], Anderson, Natarajan, and Thomas state the standard justification for this demand, “pre-specifying the analysis...is perceived to minimize bias...” This is a level of sloppy thinking that has no place in the development of statistical methodology. What does the word “bias” mean in this statement?

It cannot have the precise meaning of “bias” in statistical theory since there are only two meanings to the word. An estimator of a parameter is biased if the expectation of the estimator is not equal to the parameter. An hypothesis test is biased if the probability of rejection is less than  $\alpha$  for part of the class of alternative hypotheses. Obviously, those who believe this bit of dogma do not have either of these two meanings in mind. So, let us try to give a precise meaning to the use of “bias” in this setting.

What seems to be meant is that failure to define the method of data analysis in advance leaves open the possibility that the rejection region of the test statistic that is finally used will have probability, under the null hypothesis, that is greater than  $\alpha$ . This is sometimes called an “anti-conservative” test. Let us consider under what circumstances this is true.

It is clear that one can create such a false rejection region by carefully choosing the patients who will be entered into the analysis (e.g. picking all the treatment failures from the placebo group versus all the treatment successes from the treated group). It can also be created by using a large number of potential variables of response and choosing the one that best discriminates between treatment groups. Theoretically, one can create enough variables so the probability that the variable with max difference will fall in a rejection region is very close to 1.0. (John Tukey once opined that in medical studies the variables are so highly correlated that we are working in a space of no more than five dimensions. If this is true, then use of  $\alpha/5$  instead of  $\alpha$  more than covers this problem.) We can also create an anti-conservative test by using a peculiar null hypothesis that is easily contradicted by the data (e.g. we observe a difference in one directions for males and in another direction for females and concoct a null hypothesis that the mean difference runs the opposite ways for different sexes).

What is no so obvious is that there is a fourth way to create an anti-conservative test by looking at the data first. This is illustrated in an example due to Jerzy Neyman. We observe a normally distributed, known variance = 1, random variable,  $X=0$ , and wish to test the null hypothesis that  $E(X)=0$ . We can find a narrow band of possible values around zero whose probability is less than  $\alpha$  and reject the null hypothesis. To avoid the problem of “bias” in this sense, we need to specify the alternative hypotheses in advance.

Thus, we need to specify four things in advance of breaking the blind, the set of patients whose records will be used, the variable of interest, and both the null and the alternative hypotheses of interest. Once this is done, the method of analysis (viz., ANOVA, ANCOVA, conditional likelihood, etc.) cannot be used to “bias” the results by creating an anti-conservative test. This is easily proven under the assumption that all the methods under consideration involve test statistics that are dominated by the same underlying probability measure (Lebesgue or counting). So, the choice of method of analysis cannot be used to create an anti-conservative test.

What has been known since the early 1930's is that the choice of method can influence the power of the procedure. When regulators talk about needing to define the statistical methodology in advance to avoid “bias” they are usually thinking about the possibility of an anti-conservative test. No

one mentions power. But, if power is not a consideration, then there is a simple two-sentence SAP that can be applied to all studies: “When the data base has been frozen and the patient assignments unblinded, generate a random variable that is uniform from zero to one. Call the result significant if that random variable is less than  $\alpha$ .” This is a hypothesis test with uniform power equal to  $\alpha$ .

My greatest fear is that, in attempting to “standardize” statistical analyses of clinical studies, we often ignore the problem of power. Of course, in preparing the protocol, we go through the motions of computing sample size based on 80% pr 90% power. But, these calculations assume a particular structure to the class of alternatives (e.g. normal with constant variance and shift in the mean) which is probably not appropriate for the data that are actually accumulated. Snijders [4] has observed that every test statistic has a restricted class of alternatives against which it is uniformly most powerful on the boundary. Suppose we choose a test statistic whose restricted class of alternatives does not include the alternatives that might be expected if there is a treatment difference. Then, the power to detect a difference is less than we believe, and it will take a much larger number of patients to produce a “significant” result.

At a time when more and more new drugs are going to be aimed at “orphan” diseases (incidence less than 200,000 per year in the U.S.) and when pharmaceutical companies are competing among a small number of qualified sites to run large Phase III studies, we can ill afford to demand more patients per trial than are really needed.

As a simple example, suppose the primary measure of efficacy has an essential infimum (e.g. number of affected joints in arthritis), and suppose that effective treatment drives many patients into that infimum (zero in the case of affected joints). Then, the difference between placebo and effective treatment groups is not a simple shift in the mean but a change from a symmetric to a skewed distribution. Linear models like ANOVA are not the most powerful way to examine such a situation.

Summing up, I suggest that the fear of “bias” can be overcome by specifying in advance the patient population, the measure to be used, the null hypothesis and the alternative hypotheses, and that the class of alternative hypotheses be generated not from a convenient mathematical model but from careful consideration of what might be expected to happen if there is a true treatment difference. Once this is done, there is no need to specify the exact method of analysis in advance.

## References

- 1) Anderson, K.W., Natarajan, K., and Thomas, N. (2002) Forward, *Biopharmaceutical Report*, vol. 10, no. 2, pp 1-2.
- 2) Eckert, W., (2002) Statistical Analysis Plans, *Biopharmaceutical Report*, vol. 10, no. 2, pp 4-6.
- 3) When, W. Costigan, T., and Lindborg, S. (2002) Statistical Analysis Plan: Lilly Experiences, *Biopharmaceutical Report*, vol. 10, no. 2, pp 2-4.
- 4) Snijders, T.A.B. (1979) Asymptotic Optimality Theory for Testing Problems with Restricted Alternatives, *Mathematisch Centrum*, Amsterdam, section 3.4, pp. 64-66.

## Let's Hear from You!

If you have any comments or contributions, contact **Editor:** Neal Thomas, Pfizer, Clinical Biostatistics, Eastern Point Road/MS 8260-2227, Groton, Connecticut, 06340; Phone 860-715-0268; 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, New Jersey 08543; Phone 609-818-4299; email: [kannan.natarajan@bms.com](mailto:kannan.natarajan@bms.com).

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

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**Biopharmaceutical Report**  
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