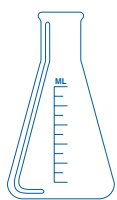


## Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

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Chair: *Steven Snapinn*

Editors: *Ersen Arseven, Demissie Alemayehu, and Anne Meibohm*

## Pharmaceutical Statisticians in the U.S.: Our Future and Our Direction

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### The Environment

The phone rang again, another executive recruiter on the line looking for qualified statisticians to fill exciting positions in the pharmaceutical industry. There are positions available on the East Coast, on the West Coast, in the Midwest, in the South, in the Southwest, and in the Northeast. Time has never been better for statisticians who want to start a career in the pharmaceutical industry or to make a career move within the industry.

The Kefauver-Harris Amendments were issued in 1962. The Amendments required drug sponsors to prove a product's safety and efficacy in controlled clinical trials in order to market the product. Since the issuance of the Amendments, the number of statisticians working for the pharmaceutical industry has greatly increased. In the 60s' and 70s', pharmaceutical statisticians played mostly a supporting role. By comparison, the fast pace of the 80s' and 90s' has created a real opportunity for statisticians to participate beyond the merely supportive role. During the past two decades, the importance of speed in bringing new products to the marketplace has really hit home among pharmaceutical sponsors. As a result, the pharmaceutical industry as a whole has devoted much resource and effort to finding ways to expedite the drug development process. On the product review and approval side, greater emphasis on speed has led to the implementation of the Prescription Drug User Fee Act (PDUFA) I & II in the United States. The same effort has also resulted in the publication of many guidance documents by the US FDA as mandated by the FDA Modernization Act.

With the additional resources provided to the FDA under PDUFA I and II, FDA has been able to shorten its product review time. The IMS America data suggested that post-1990 product launches accounted for 43% of the prescription drug sales in 1997. Between the time PDUFA I became effective in 1994 and the end of 1998, 172 new molecular entities were approved. Considering that about 10 to 15% of applications were reviewed but not approved, an even higher number of applications for new molecular entities were submitted. This statistics reflects an extremely active industry where being the first of a new class on the market is as important as the characteristics of the product itself.

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As the population ages and our race to meet the unmet medical need reaches a record high level, so will our expenditure on medicine. The Pharmaceutical Research and Manufacturers of America (PhRMA) represents leading research-based pharmaceutical and biotechnology companies in the US. According to PhRMA's record, 2.5 billion prescriptions were filled for medicines that relieved pain, fought infection, saved lives and enhanced the quality of life for millions of patients in 1998. This figure is expected to grow higher as the US government considers Medicare reform, hoping to provide drug coverage for the nation's senior citizens.

Consequently, the search for safer and more efficacious pharmaceutical products will continue to intensify in the future. PhRMA reported that its members currently invest over \$24 billion annually on the discovery and development of new medicines.

The great progress in developing pharmaceutical products has created a real need for innovative trial designs and more complicated analyses for trial data. Statistical methodology research related to clinical trials has flourished and populated many statistical journals in the last 2 decades. Much attention has been paid to group sequential and adaptive designs, multiple comparison procedures, and methods for handling missing data. Recently, effort on using simulation to facilitate the selection of dose and schedule has gained momentum in the exploratory phase of pharmaceutical product development.

Kroll (1998) reported a more than 10% increase in pharmaceutical sponsors' annual spending on research and development. The increased spending has led to a 21% increase in the annual revenues of Clinical Research Organizations. On the other hand, the overall R&D employment rate increased by only 3-4% annually for the past three years. As a result, pharmaceutical industry is starving for qualified personnel, including statisticians.

In the current bustling environment for pharmaceutical research and development, job opportunities for pharmaceutical statisticians are plentiful. Statistical groups of moderate size are either present or forming in major pharmaceutical companies. Within the American Statistical Association, the Biopharmaceutical Section has become the second largest section with membership continuing to climb. The mass created by pharmaceutical statisticians is gravitational. The number of journals dealing with statistical issues related to drug development is impressive. The AMSTAT NEWS routinely contains ads for pharmaceutical statisticians. Whichever way I look, I see opportunities for pharmaceutical statisticians. The question is—are we taking advantage of this unprecedented opportunity to increase our influence and contribution?

## How Are We Doing?

As statisticians in the pharmaceutical industry, we pride ourselves on a variety of contributions to the development of pharmaceutical products. At the study-planning stage, we can help our clinical colleagues solidify the objectives of a study and translate scientific questions into testable hypotheses. We can share, with our current clinical study

team, our experience acquired from supporting other therapeutic areas. Furthermore, we can establish quantitative criteria for decision-making and optimize design to facilitate the estimation of treatment effect. At the study-conduct stage, we work hard to ensure that data collection is in line with the study objectives and that interim analyses maintain the integrity of the study; we can provide guidance on mishappenings to minimize bias and we check the design assumption for possible sample size re-estimation. We become gatekeepers for tasks where responsibility is not clearly defined. At the study-analysis stage, we help interpret findings from a probabilistic perspective and help translate numerical output into medical language. We document methodology, extract useful relationships and supply an objective and realistic views of the results. We can help make decisions according to scientific principles and suggest further areas for exploratory analysis and future investigation. Some of my colleagues compare statisticians to the crazy glue that helps gel the whole study team together as one team.

Gould (1999) discussed the evolving roles of statisticians over the past few decades. Gould discussed the need for statisticians to help define the strategies for common global development of pharmaceuticals with the end results such as the desired claim structure in mind. For this role, statisticians are challenged to use their training and expertise at the level where the structure of the development strategy is laid out. Gould also challenged statisticians to spearhead the implementation of new guidelines for clinical trial design and analysis. The latter includes standard operating procedures within each organization as well as strategies for introducing new methodologies. To be successful, statisticians need to be keenly aware of the environment in which we function. In addition, statisticians also need to continuously adapt to this constantly changing environment.

O'Neill (1998) described how the availability of statistical leadership in regulatory agencies and pharmaceutical industry has made advances in drug development and regulatory decisions for pharmaceutical products possible. As problems become more complex and planning becomes more crucial, statistical thinking will increasingly become more in demand. O'Neill challenged pharmaceutical statisticians to pull collective resources to meet the problems facing us in the next millennium. According to O'Neill, we should always ask whether we are involved in the most important problems where the influence of statistical approaches positively advances public health.

All of the above pertains to areas where statisticians could and should contribute. My questions are: Are we seeking out the most important problems to work on and feeling proud day after day that our statistical knowledge has positively advanced public health? Are we contributing at the level that has the highest added value to our respective companies? Are we routinely helping strategize for global development of pharmaceuticals? How many of us are participating in the crafting and implementation of new guidelines? Do we stand ready to meet the challenges raised by Gould and O'Neill?

At the day-to-day level, how are we doing? Are we usually acting in a narrow capacity, becoming content with our individual technical role? Or do we have a prepared mind, ready for opportunities to contribute at a higher level? Do our colleagues benefit substantially from our collaboration so that they gladly invite us back time after time for more joint adventures?

While statisticians enjoy a booming job market, I often wonder how much of the market prosperity is due to regulatory requirements for statistical rigor and auditable documentation. An ensuing question is – if it were not for the requirements imposed by regulatory authorities, how many statisticians would be employed by the pharmaceutical industry? When statisticians' presence is required by regulatory agencies, statisticians are often regarded as a police force with the primary responsibility to ensure the integrity and validity of the data. But, do members of the team appreciate our presence? Because of the policing role, sometimes there is the fear that statistician will only be there to criticize and therefore discredit researchers' work and effort. The perception of this negative professional role can discourage researchers from inviting statisticians to join in their experimental efforts. This is unfortunate because many statisticians possess a great deal of knowledge about experimental design, bias reduction, and data analytic methods that could be of great value to other researchers.

Even when statisticians are not perceived as a policeman, do our non-statistical colleagues need to be reminded repeatedly of the value of statisticians as a scientific partner, or do they automatically think of us when crucial decisions are being made? I often compare statisticians to guests at a host's house for a party. Assuming the house is sound and the party enjoyable, we would like to be invited back to the host's house. The best way to ensure that this will happen is our demonstrated ability to add to the success of the party.

As each of us fulfill our individual job responsibilities, are we also concerned with the image of our profession as a whole? As a statistician, when we respond to the challenge of a technical role expected of us by our pharmaceutical colleagues, we are also helping them shape their image of us. Donahue (1999) said it all when he classified information-providers into three categories: technicians, tacticians, and strategists. Donahue defined a technician loosely as someone who uses simple or complex process learned through years of hands-on training and experience to answer questions of a technical nature. A tactician addresses issues that dictate the direction of future technical work while a strategist tackles large-scale issues that affect the development and business strategies both now and in the future. Donahue examined the type of questions that most statisticians are answering today and concluded that while occasionally serving as tactician and rarely as strategist, the typical statistician in the pharmaceutical industry today is a technician.

The current ASA President Jonas Ellenberg (1999) examined the very same question of whether statisticians are being largely viewed as technicians or partners in our collaborative efforts with other disciplines. Ellenberg's definition of technicians includes those who apply advanced

statistical methodology. Ellenberg concluded that based on his observation, we are for the most part viewed as technicians. Ellenberg argued that the perception of statisticians' being technical consultants is harmful to our profession since better analyses and more methodological advances are more likely to come from true collaborations than from superficial technical consultations. Besides, superficial technical consultation limits our potential contributions.

I cannot speak for everyone, but most of us want to participate in major decision making that affects our jobs. I have heard statisticians lamenting over not being included when decisions are made. The feeling of being left out may be more pervasive than we care to admit.

Part of the above problem may be related to the dichotomy among statisticians between data analysts who are content with the knowledge on how to perform certain statistical tests and statistical scientists who look to what the statistical profession can best offer to the scientific world. The truth is - when we behave as a technician, we will be treated as a technician. If we only care about conducting t-tests, we will only get invited to perform t-tests. Our presence might be guaranteed because of regulatory requirement, but this requirement does not automatically translate to respect and invitations to join in high-level decisions. Respect and trust is something that each of us needs to earn with quality deliverables!

Donahue (1999) suggested that one possible reason for our functioning as a technician is our desire to maintain control of our technical world. He indicated that when we are busy burying our business partners in piles of paper through reports and tables, when we are keeping quiet our secrets of sample size and power, when we are insisting that all the P-value and text be first blessed by statisticians, and when we are smothering people with mind-numbing complexities of multiple comparisons and other statistical jargons, we are roping ourselves to the technical statistical world and implicitly telling others that ours is only the technical world and it is beyond the comprehension of others.

There are reasons why many of us are more comfortable staying with the technical role we have been playing. For one thing, we are more familiar with the technical world and we know the language. It is often scary to step out of one's familiar operating environment into another one where decision often carries a higher degree of risk. As statisticians, we have learned decision theory based on well-specified rule and cost function. But in the real world, conditions are often unknown and our nice probability models often do not apply directly. To be able to function effectively in such an environment, one needs to be able to improvise and adapt. The latter might take many years of experience and learning for one to feel comfortable. It is possible that for some, the comfort level will never reach a minimally operable level. Unfortunately, the ability to lift oneself to a higher ground will ultimately determine the value of one's contributions.

## What Should We Do?

I posted a note to our Section's (Biopharmaceutical Section) electronic list last year seeking input to the general

issue discussed in this article. Specifically, I wanted to get a sense of our list members' perception of our role and what we, as a group, can do to increase our contribution and enhance our image.

One of the areas identified by a colleague is the apparent imbalance between research in statistical methods and the implementation of useful statistical methods. Even though t-test and analysis of variance are easy to explain to our non-statistician colleagues, they often are not sufficient to handle the increasingly complex clinical trials with many complicated issues. The same colleague recommended a "back-to-back" publication strategy of papers on new methodology and on applications of the methodology to real-life examples. To further the applications of new statistical methodology to drug development, statisticians in pharmaceutical industry need to work with their counterparts in the regulatory sector. For this effort to be successful, statisticians working in the regulatory sector need to be receptive to new ideas and new methodology. I personally do not feel this to be a problem since our statistical colleagues at the U.S. FDA have published many excellent research papers during the past 2 decades.

Many responses to my note suggested that the ability to communicate, both orally and in writing, is crucial to a statistician's successful collaboration with other disciplines. This is understandable for a discipline that requires a great deal of listening, discussion, and negotiation. There is a continuing request from the industry to academic institutions to place more emphasis on communication skills during the formal academic training. Knowing how to ask, when to ask, and what to ask in an effective manner is not only necessary to get the job done, but will also help shape our collaborators' impression of us.

To expand our contribution to the drug development process, Donahue (1999) suggested that we expand our technical role into the strategic and tactical arenas. According to Donahue, statisticians need to show that we have something else beyond reports and tables to contribute to the project. We need to be willing to delegate basic tasks such as table validation to technicians and invest a greater portion of our energy on endeavors with greater impact. Branching out of our familiar territory can be scary. Some will choose to stay with the routine responsibilities because the latter are what they are familiar with. However, unless we can challenge ourselves to step out of the circle we have drawn for ourselves, we will always be handicapped and limited by the invisible boundaries.

It is important that we have skills beyond sample size calculation and the analysis of variance. The mindset of keeping sample size calculation a secret to ourselves for fear that others might otherwise not come to us is detrimental to our becoming strategic. Donahue strongly suggested that we freely share such secrets with other collaborators since only when we do so, can we free ourselves from the confines of technical skills and let others see us from a different light. Furthermore, with the proliferation of statistical software packages, an inquisitive researcher does not have to go very far to calculate sample size themselves and to conduct an analysis of variance.

While there is always a need for statisticians who choose to contribute in the capacity of a technician, we need to be acutely aware of the difference in the contribution levels between technicians and strategists. Regardless of the role we choose to play, we need to continue to improve ourselves, always looking for opportunities where we can make a positive impact.

I have always thought that statistics is both an art and a science. Often, there are many different ways to approach a situation without sacrificing statistical principles. We need to be flexible and adaptable; we need to be congenial and assertive; we need to be understanding and firm; we need to be open-minded and willing to go the extra miles to learn the basics of our collaborators' discipline. Most important of all, we need to work on a strong alliance with our collaborators, winning their trust and respect with demonstrated performance through our individual involvement.

## Conclusion

What will it be? Are we letting others mold us into something we may not want to be or should we work individually and collectively to define our own role? What is the fuel we need to blaze our own trail?

There are plenty of workshops and short courses that can help us sharpen our technical skills. What is lacking is the necessary training to prepare statisticians for the uncertainty and unknown beyond the technical world. The latter includes non-technical skills necessary for statisticians to work effectively in a team-based environment. Ironically, many statisticians are experts on handling variability and uncertainty described by well-defined distribution; but are ill prepared for a decision world that lacks a probability model.

Technical tools are easy to learn; so are computer software packages. What is not so easy to implement is a self-engineered development plan to broaden one's circle of influence. Chuang-Stein (1996) emphasized the importance of individualized on-job training for pharmaceutical statisticians. According to Chuang-Stein, sustained training, both technical and non-technical, can help expedite a statistician's gaining independence and maturity at the work place.

Certification issue has been discussed for several years within the American Statistical Association by now. Will a certificate in our office automatically translate to long-lasting respect? I am inclined to say "no" as a certificate that is not followed by an actual show of ability is of no consequence. What brings a collaborator back again and again on their own is our ability to add positively to the working relationship.

The world is not black and white; it has many shades of gray. No two statisticians are and will ever be the same. Each of us needs to be aware of our strengths and weaknesses, and make a conscious decision on our pathway. The decision includes the kind of playing field on which we would like to operate eventually. Since opportunities come to a prepared mind, we will miss out on opportunities unless we have given this issue some long and hard thoughts beforehand.

Are we happy where we are today? Are we at the level of professional recognition we would like to receive? Within

our individual corporations, are we being included in important decision making on a routine basis? Or have we learned to accept the status quo? I am glad to report that many responders to my e-mail note expressed satisfaction and rewarding experience at their work place. It is great to know that job satisfaction is attainable for many of our industry colleagues.

On the other hand, many of us have not taken much time to think about the above questions. From time to time, I have heard complaints about statisticians being left out of the crucial information loop. Unfortunately, these complaints did not always translate into actions that could change the situation. Instead of complaining, it will be more useful if we can address questions such as our corporate image and our relationship with our collaborators to help us understand why we were experiencing what we did.

I have no doubt that many statisticians are doing exactly what they consider important tasks for statisticians. I personally have witnessed such rewarding alliance, especially in the academic setting where statisticians are equal scientists to their research partners. In the latter case, the collaboration is genuine. On the other hand, I have also seen statisticians functioning more as a processor, pushing papers along the drug development production line and feeling unappreciated at the same time.

Regardless of our academic training and our career aspiration, I would like to promote in this paper the need for statisticians to look ahead and help shape the direction of their job responsibilities. If through this paper, I can raise the awareness among statisticians of the distinction between technicians, tacticians, and strategists, I consider this paper a success.

To a great extent, our destiny is in our own control. We are all free to choose where we are heading. I am hoping that we are all willing to invest time and effort to form a strong strategic alliance with our collaborators. I am also hoping that we are also willing to invest in our own growth and maturity. The latter is essential for us to contribute beyond the level of technicians!

## References

- Chuang-Stein, C. (1996). "On-the-job Training of Pharmaceutical Statisticians." *Drug Information Journal*, 30(2), 351-357.
- Donahue, R. (1999). *Some Commentary on Maximizing the Statistician's Value to the Pharmaceutical Industry*. Submitted for publication.
- Ellenberg, J. (1999). "Statisticians and Communication." *Amstat News*, Issue #261, 8-9.
- Gould, A.L. (1999). *The role of Statisticians in Global Clinical Development: A US Industry Perspective*. Submitted for publication.
- Kroll, J. (1998). "Keeping Pace with Industry Growth. Building a Strong Employee Base Poses Challenges." *Applied Clinical Trials*, 7(7), 27-32.
- O'Neill, R.T. (1998). "The Status and Impact of Statistical Principles and Methodology in Facilitating the Availability of New Therapies: A Regulatory Perspective." Presented at the 1998 ICSA Applied Statistics Symposium.

## Letter from the Chair

Steven Snapinn

This is the column where the outgoing Chair gets to brag about all the accomplishments of the Section during the past year. In fact, as the last Chair of the 1900's (no way am I getting mixed up in the date of the new millennium debate) there's some temptation to focus farther back and recount the Section's accomplishments throughout its history. I'm going to resist that temptation, though, since Bob Davis has agreed to put together an official history of the Section, and I'm sure I couldn't compete. Be on the lookout for Bob's history of the Section in a future issue of the Biopharmaceutical Report. I can guarantee that it will be informative, entertaining and irreverent. So I'll just report below on some of the Section's major accomplishments during 1999 and the names of the people behind these activities. The Section is blessed with a large number of capable and hard-working volunteers, and I'm happy to be able to thank them in this column.

As I'm sure you know by now, the Section recently crossed the 2000-member milestone and is the 2nd largest Section of the ASA. A large part of the credit for our increase in membership goes to the work of the Membership Committee, chaired for the past several years by Phil Pichotta and supported by David Carlin and Mark Munsell. Some of the innovations the committee has instituted include sending letters to lapsed members and to pharmaceutical statisticians who are not members, and distributing an identifying sticker and a Section program to Section members at the JSM.

And speaking of the Section's program, Christy Chuang-Stein put together an excellent set of sessions and courses at ENAR and the JSM. The Section sponsored 3 invited paper sessions at each meeting, plus 8 special contributed paper sessions, 12 regular contributed paper sessions, 3 short courses and a workshop at the JSM. I've seen the evaluation forms for the short courses and workshop, and all were very well received. The Section also sponsored 9 luncheon roundtables, organized by Sandy Heft.

As in past years, at the JSM the Section gave awards for Best Contributed Papers and Best Student Papers. A considerable amount of effort goes into organizing and administering these awards. Thanks go to Lukas Makris for collecting and compiling the evaluation forms for the Best Contributed Paper awards, and to the Student Paper Committee (Naitee Ting, Demissie Alemayehu, Tuli Cnaan, and Tom Bradstreet) for reading and evaluating the students' contributions.

The 4th annual FDA/Industry Workshop took place on September 30 and October 1, co-sponsored by the FDA and the Biopharmaceutical Section. The theme of the workshop was Statistical Issues for the New Millennium, and it was once again a big success. The program committee for this meeting included Biopharmaceutical Section Executive Committee members Nancy Smith, Ralph Harkins, Bob Small, Lukas Makris, and Sandy Heft.

Thanks to Ersen Arseven and the other Biopharmaceutical Report editors, Demissie Alemayehu and Anne Meibohm, for their hard work putting together these pages. I can sympathize with the problems they must have dealing with contributors who never do what they promise and are always late. (If you are reading this, that means that Ersen managed to hold the presses for me.) Denise Roe, the Section's Publications Officer, helped put together the Section's Proceedings, and got an informational article into nearly every issue of Amstat News.

The Section's electronic mailing list, moderated by Sally Greenberg, made great progress in 1999 and has generated some interesting discussions. The Section's web site <http://www.best.com/~asabp/index.htm> thanks to webmasters Kalyan Ghosh and Laura Hawthorne continues to be a useful source of information. Thanks also to the Fellows Committee, (Larry Gould, Bruce Rodda and Charlie Goldsmith), for their support of Section members' nominations for ASA Fellow.

Of course, with all of these activities going on, managing the budget and keeping meeting minutes is no small task. I thank the Section's Secretary/Treasurer, Sally Greenberg, for handling all these details. The Section entered 1999 in reasonably good financial shape, and Sally assures me that I've only managed to squander a relatively small fraction of the Section's resources.

Finally, thanks to our Council of Sections representatives Chuck Davis (in his final year) and Nancy Smith, and a special thanks to outgoing Past Chair Ken Koury for his many years of service. The Section is certainly in great hands for the year 2000. Tom Capizzi will take the reins as Section Chair and Bob Small as Program Chair. Newly-elected members joining (or re-joining) the Executive Committee are Chair-Elect Jeff Meeker, Program Chair-Elect Keith Soper, and Council of Sections Representative Ralph Harkins. Best wishes to all for the new millen-... I mean, Year 2000.

## Roundtable Discussions

### Use of Surrogate Markers in Clinical Trials

**Leader: Robert C. Kohberger**  
*Wyeth-Lederle Vaccines*

This roundtable discussion focused on three issues in the use of surrogate markers in clinical trials—how to define a surrogate marker, how to validate a surrogate marker, and how to use surrogate markers in a regulatory submission. Participants included individuals from the pharmaceutical industry, academics, and consulting companies. Experience within a regulatory agency was also represented. It was strongly agreed that both the definition and

use of a surrogate marker are greatly dependent on the underlying science of the process under consideration. Clear scientific justification of the marker is required regardless of the statistical issues. The failures of surrogate markers were discussed (Fleming and DeMets, 1996) with additional examples brought forth from the participants. The criteria for validation of a surrogate marker were discussed. There was little disagreement with the Prentice criteria for validation (Prentice, 1989), but few of the participants had an occasion (or dataset) where a surrogate could be validated using these methods. Comments from a regulatory perspective were that, if at all possible, surrogates should be avoided for pivotal trials. The industry perspective was that surrogates are most useful in early phase trials, but for pivotal trials a true clinical endpoint is most desirable. It was noted that in order to validate the surrogate marker a true clinical endpoint is required so that for a unique therapy, in practice, the validation occurs too late to be of value in the development process for that particular product. The general consensus was that surrogate markers remain a problematic issue. The clear failures of many surrogate markers indicate that validation of the marker is required. However, the necessary conditions for validation are such that validation (or failure of the marker) occurs late in the development process.

### References

- Fleming, T.R. and DeMets, D.L. (1996). "Surrogate Endpoints in Clinical Trials: Are We Being Misled?" *Ann Intern Med* 125, 605-613
- Prentice, R.L. (1989). "Surrogate Endpoints in Clinical Trials: Definition and Operational Criteria." *Statistics in Medicine* 8, 431-440.

### Demands for Flexibility in Clinical Trials Require Innovative Approaches

**Leader: George Y.H. Chi**  
*Division of Biometrics, CDER, FDA*

The luncheon roundtable participants were all from the pharmaceutical industry. After introducing each other around the table, we discussed interim analysis issues in general, and the problem of potential bias being introduced as a result of interim analyses.

Interim analysis is an example of a demand for flexibility in clinical trials. History shows that the early development of interim analysis is a product of the demand for early analysis of efficacy data. This demand comes from an ethical imperative - the desire to terminate a trial early if significant and unexpected treatment benefit is seen, so that other patients enrolled in the trial can be given the effective treatment earlier. Ethical demand may be justified in mortality and serious morbidity trials. However can interim analyses be justified in non-mortality and non-serious morbidity trials?

This issue is particularly relevant in most of the fixed, small-to-moderate sample size trials. We are often faced with the demand for interim analysis in such trials on grounds other than ethics, such as administrative reasons. We have seen trials that were terminated after such interim looks despite the sponsors' assurances to the contrary that they would not be terminated. So for this kind of trials, is interim analysis really justified? How should we handle such situations? Would the O'Brien-Fleming type spending function be appropriate in these situations? We shouldn't encourage interim looks of the data, and should delay the interim look as much as possible or not do it at all. So this is an example of a demand for flexibility in clinical trials, where the application of some of the traditional group sequential procedures may not be entirely appropriate. Other innovative approaches will be needed.

Other demands for flexibility in clinical trials have been the subject of a recent Harvard/Schering-Plough workshop. These demands have been described as design modifications while trials are still on going. One of the more common demands is for sample size re-estimation as a result of an interim look. Another demand is for dropping one or more arms as a result of an interim look. The issue regarding sample size re-estimation has recently been addressed by Cui, Hung and Wang (1999) within the context of a group sequential trial. Similar issues have been addressed by Bauer and Köhne (1994), Proschan and Hunsberger (1995), Chi and Liu (1999), Liu and Chi (1999) within the context of a fixed sample size trial. Issues related to dropping treatment arms have recently been addressed by Sill and Sampson (1999) in a similar setting.

The point is that these modifications will invariably result in an increase in the overall type I error because the subsequent decisions are based on the interim outcomes. So appropriate innovative methods are needed to address these issues satisfactorily. One cannot simply apply some analysis without addressing the issue of the inflation of the overall type I error. Participants were reminded of a special topic session on "Designed Flexibility in Clinical Trials" the next day that is devoted to this specific topic. It was pointed out that it is clear from the topic of this special session that such modifications should be designed into the study. Granted that one cannot always anticipate the unexpected, but at least designed flexibility will avoid or minimize many of the problems we encounter today in clinical trials.

An associated issue with interim analysis, is the potential introduction of operational bias subsequent to such interim analysis. This issue needs to be studied in the fixed, small-to-moderate sample size trials. An appropriate guideline on the conduct of such interim analysis will be needed.

## References

- Cui, Hung and Wang, (1999). "Modification of Sample Size in Group Sequential Clinical Trials." *Biometrics* 55, 853-857
- Bauer and Köhne (1994). "Evaluation of Experiments with Adaptive Interim Analysis." *Biometrics* 50, 1029-1041.

Proschan and Hunsberger (1995). "Designed Extension of the Studies Based on Conditional Power." *Biometrics* 51, 1315-1324).

Chi and Liu (1999). "Attractiveness of the Concept of a Prospectively Designed Two-Stage Clinical Trial." *Journal of Biopharmaceutical Statistics* 9, 537-547.

Liu and Chi (1999). "On Sample Size and Inference for Two-Stage Adaptive Design." Presented at the JSM Baltimore.

Sill and Sampson 1999. "Simple Two-Stage Drop-the-Losers Designs." Presented at SM Baltimore.

## The Impact of ICH Guidelines on Protocol Development

**Leader: Imogene Grimes**

*Pfizer, Inc.*

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an ongoing project since 1989, focused on the harmonization of technical requirements for registration during the Phase 1 of the project. In this effort, the ICH defined expert working groups and charged them with developing guidelines for specified aspects of clinical research. The E-series of guidelines from the efficacy expert working groups were the focus of this roundtable discussion. Most of the participants were statisticians or data managers from the pharmaceutical industry.

In order to ensure a common base of understanding of US practice and the relative role of the guidelines, the hierarchy of documents that delineate the expectations of regulators was discussed:

- Laws passed by congress (e.g., The FDC Act);
- Regulations issued by the FDA that interpret the laws (e.g., 21CFR312 and 21CFR314);
- Guidelines issued by the FDA; and
- Guidances issued by the FDA to represent current thinking of the Agency—are not intended to be binding on the public nor on the Agency.

To facilitate discussion, copies of three ICH guidelines were distributed to participants: E6, the consolidated Guidelines for Good Clinical Practice (GCP); E9, the consensus guideline on Statistical Principles for Clinical Trials; and E10, the draft consensus guideline for Choice of Control Group in Clinical Trials.

Discussion opened with general observations about the direction given by the ICH for protocol development and associated development of the statistical analysis plan (SAP). Guideline E6 includes some key principles of GCP and several of them were discussed at the roundtable. Principle 2.8 states, "Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)." As discussed, this principle is consistent with other direction given in the guidelines, that all individuals involved with the clinical trial (including the development of the protocol, data management, analysis, and reporting) should be qualified to

perform their respective functions. Statisticians should be responsible for statistical aspects of the protocol, physicians should be responsible for medical aspects, and data managers should be responsible for data management. As was discussed, the intention is not that a statistician needs to have a Ph.D. in order to write the statistical methods section of the protocol, but it should be written by a statistician as opposed to a physician.

A key data management principle is described in Principle 2.10, "All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification." The broad-based impact of this principle was briefly discussed.

A discussion ensued about the differences between confirmatory analyses and investigational analyses. Particular attention was given to E9, which clarifies these differences and the respective roles of these analyses, pointing out that confirmatory studies have confirmatory hypotheses, but confirmatory studies may also have investigational hypotheses. Investigational studies can only have investigational hypotheses.

The role of covariates in integration of scientific evidence was discussed. One statistician mentioned that for one study in a project, a certain set of covariables was identified as important for inclusion, and, in another study, a different set of covariables was identified. Other participants indicated that they had similar experiences.

Attention was given to Guideline E9, which gives direction for covariate adjustment. In Section 5.5, the ICH advises that "...The particular statistical model chosen should reflect the current state of medical and statistical knowledge about the variables to be analyzed as well as the statistical design of the trial. All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified..." ICH encourages statisticians to identify a priori variables that should be included as covariables in the primary analysis. Step-wise procedures have historically been discouraged for the primary analysis, due to the study-dependent nature of the model. As FDA speakers have explained in the past, there may be 30 variables collected in a study that may be considered potential covariables, and there may be another 200 variables that are more important, but are not collected in the study. For the primary analysis, the models, including particular covariables, should be completely specified in the plan. Clinical trialists tend to appeal to randomization and laws of large numbers to reduce bias. Covariables identified at the analysis stage have an important role in the complete analysis of a study, but the primary analysis should follow the plan.

The discussion included emphasis on ICH encouragement that the purpose of many exploratory analyses may be to ensure robustness of the conclusions and to ensure that conclusions are preserved when adjustments are made for covariables.

Advice from the ICH was considered jointly with advice from the FDA. In some communications from the FDA, there have been specific statements advising against the use of step-wise procedures for primary analyses. For the integrated summaries, a model proposed for an overall, integrated analysis should make sense for all of the studies

included in that analysis. Section 5.5 of Guideline E9 gives some advice on this point: "Within...the statistical analysis plan, there should also be an outline of the way in which data other than the primary and secondary variables will be summarized and reported. This should include a reference to any approaches adopted for the purpose of achieving consistency of analysis across a range of trials..."

In summary, the roundtable discussions included a strong appreciation for the contribution of the ICH guidelines, as they give guidance for development of the protocol and the associated SAP. Particular benefits gleaned from the issuance of the guidelines include:

- Glossaries, that standardize language;
- Written scientific and statistical principles;
- Documentation for standards for statistical approaches; and
- Clarification of key issues, such as the difference between confirmatory and exploratory analyses.

## Section News

### Minutes of ASA Biopharmaceutical Section

#### *Executive Committee Meeting*

*March 29, 1999, Atlanta, Georgia*

#### **Attendees:**

Demissie Alemayehu	Sally Greenberg	Frank Shen
Tom Capizzi	Sandy Heft	Bob Small
Avital Cnaan	Ken Koury	Nancy Smith
Chuck Davis	Lukas Makris	Steve Snapinn
Kalyan Ghosh	Phil Pichotta	

#### **Appointments**

Steve Snapinn announced that Curtis Wiltse had resigned as Program Chair-Elect and that Bob Small has agreed to accept the position.

#### **Minutes from the October 29, 1998 Meeting**

The minutes of the October 29, 1998 Executive Committee meeting held at Schering-Plough Corporation in Kenilworth, NJ, were approved with corrections of 3 minor typographical errors.

#### **Treasurer's Report**

Sally Greenberg reviewed the 1999 financial statement for 1/1/99 through 3/31/99 from ASA. The Section will

exceed its food budget this year. The following bills don't appear in the financial report: (1) Section ever paid for the room or food for the 1998 Executive Committee Meeting at the ENAR Meetings, (2) 1998 poster donation, (3) bills for the Section's Internet account.

**Assignment:** Steve Snapinn will order food for 150 for the Section's mixer at the JSM.

**Assignment:** Ken Koury will check to see whether he has an outstanding bill for the room and/or food at the 1998 Executive Committee Meeting at the ENAR Meetings.

**Assignment:** Sally Greenberg will remind the ASA office about the Poster donation and submit bills for the Section's Internet account. She will also increase the amount for food in the 2000 budget and review the Section's 1999 actual vs. proposed expenses overall.

## 2000 ASA Budget

The ASA Office has sent out a memo soliciting input for new initiatives for inclusion in the 2000 ASA Budget. These need to be submitted to Steve Porzio by 4/30/99. Phil Pichotta proposed 2 initiatives, both of were supported by the Executive Committee supported.

**Assignment:** Phil Pichotta will submit proposals to the ASA office covering the following 2 topics: (1) A follow-up to the salary survey and (2) Surveying recent graduates getting a recent statistics degree (where are they going, etc.).

## ENAR Program

Christy Chuang-Stein reported that the Biopharmaceutical Section is sponsoring 3 invited paper sessions at this year's ENAR Meetings. The three sessions are "The Use of Computer Intensive Methodology in Drug Development - Using the Tools You Have to Answer the Question You Really Care About" organized by Sandy Heft, "The Use of Meta-Analysis in Treatment Evaluation and Drug Development" organized by Sue Marcus, and "Multiplicity Issues in FDA Submissions" organized by Greg Campbell.

## AMSTAT News and Proceedings

Denise Roe reported on the status of our AMSTAT News column and the 1998 proceedings.

### AMSTAT News Submissions:

The articles for 1999 are as follows, with the same sequence to be followed in 2000.

#### January 1999

1998 Section Highlights Kenneth Koury

#### February 1999

Member Benefits Philip Pichotta

#### March 1999

Biopharmaceutical Sessions at Christy Chuang-Stein  
1999 ENAR Meeting &  
1999 Joint Statistical Meetings

#### April 1999

Biopharmaceutical Report Anne Meibohm

#### May 1999

Electronic mailing list Sally Greenberg and  
& web site Kalyan Ghosh  
Announcement of Fall Workshop Ralph Harkins

#### June 1999

1999 Joint Statistical Meetings Christy Chuang-Stein  
Overview  
1998 Best Contributed Paper Sandy Heft  
Award

#### July 1999

1999 Joint Statistical Meeting Christy Chuang-Stein  
Calendar  
Announcement of Fall Workshop Ralph Harkins

#### August/September 1999

Winners of 1999 Best Student Naitee Ting  
Paper Competition

#### October 1999

Executive & Business Meeting Sally Greenberg  
Summary from 1999 JSM

#### November 1999

Student Paper Competition Naitee Ting  
Announcement & Procedures

#### December 1999

Summary of Fall Workshop Ralph Harkins

### 1998 Biopharmaceutical Section Proceedings:

The 1998 Biopharmaceutical Section Proceedings are being printed. There are 53 papers with 284 pages. Among the sections that publish proceedings, we are second in the number of papers (Survey Research Methods is first with 172). Across the various Sections of ASA, there were fewer papers sent for inclusion in the proceedings (582 papers in 1998 versus 737 papers in 1997). The Biopharmaceutical Section, however, stayed relatively constant (53 papers in 1998 versus 56 papers in 1997).

**Post-Meeting Note:** The 1998 Proceedings actually contained 52 papers, rather than 53 papers.

There was Executive Committee discussion as to whether we should accept papers for publication in our Proceedings that are not presented at one of our sessions. It was decided that this should be done if both the Program Chair and Section Chair felt this to be appropriate. For example, a paper that was originally submitted to our Section, but which we moved to another session for scheduling purposes, might be such a candidate.

## Biopharmaceutical Report

Demissie Alemayehu provided an update on the Biopharmaceutical Report. The last issue for 1998 was delayed until early 1999 due to a change in the lead article. However, it has been 1.5 months since the lead article was submitted (other articles were submitted in December), and, due to changes in personnel and responsibilities at the ASA Office, the current issue is still not available.

**Assignment:** Steve Snapinn will call Mary Fleming (Director of Services, etc. at the ASA office) to help ensure that this is prevented from happening in the future.

**Post-Meeting Note:** This issue was available on the web site in April, and hard copies were received by Section members in June.

Work is under way for the summer issue. Jim Bergum will be the author of the lead article. Demissie Alemayehu asked for clarification of ASA's publication policy with respect to presentation (not publication) of the content of the article before publication in Biopharmaceutical Report. The Executive Committee thought that this was fine.

There will be two more issues published this year, totaling three.

There was some discussion as to whether we should be converting to publishing an electronic copy rather than a paper one or offering members a choice. It was felt that we should stick to publishing both paper & electronic versions for the immediate future. However, this will be investigated for the future.

The Biopharmaceutical Report needs more news, short notes, etc. for the next few issues.

**Assignment:** The Editors of Biopharmaceutical Report will post a notice in the Section's AMSTAT News column soliciting for more articles for the Biopharmaceutical Report.

### Electronic Mailing List

Sally Greenberg provided an update on the Electronic Mailing List.

The Advertising Policy has been implemented. So far this policy has been going smoothly. There have been only 2 minor problems so far: not getting info as an ASCII file (somewhat common) and confusion as to the difference between a mailing list and a web site. Executive Committee Members (and others) should refer people to Sally Greenberg for clarification if needed.

There was the second e-mail infinite loop last week. Sally Greenberg provided several ways to get around this problem, but all create other problems. It was decided to leave the list set-up alone, but to remind members about auto-replies.

**Assignment:** Sally Greenberg will send out an administrative message to the mailing list reminding them about problems with auto-replies.

As of 3/23/99, there were 126 people subscribed to the ASABIOPHARM Mailing list, including 9 from foreign countries, 18 from universities, 4 from US government agencies, and 95 from industry or private Internet Service Providers. The companies with the largest list membership are Merck/Astra Merck (17), Pharmacia-Upjohn (8), and Proctor & Gamble (5).

### Web Site

Kalyan Ghosh has moved the website to its new home: <http://www.best.com/~asabp>

This is the same account that the mailing list is run from. Photos of all new Executive Committee members will be added to the website.

**Assignment:** Kalyan Ghosh mentioned that the visitor counter on the site was no longer functioning, but that there is one available for \$5/month. The section approved the additional expense if Kalyan Ghost thought that it was needed.

The Executive Committee noted that the new web site looks great!

### Membership Committee Report

Phil Pichotta reported from the Membership Committee. The Section now has 2048, exceeding 2000 members for the first time. We are one of the few sections that is growing. We are second to the Stat Computing Section (which has 2329 members). However, we have only 4 corporate members.

The Membership Committee has updated the Biopharmaceutical Section Brochure. In a membership drive, 35 companies/organizations were contacted and 17 responded. 415 statisticians who were not Biopharmaceutical Section members of 627 total statisticians were invited to become members by personal letter and flyer.

The current membership list has been added to the Section website. Phil Pichotta has been going through numerous gyrations to get the membership list from the ASA office in a usable format. The names of the 4 corporate members have also been added to the Section Website, and a link can be added to their Corporate websites.

The Membership Committee plans to continue the Membership Drive as time permits. In addition, they plan to identify ASA Corporate Members in biopharmaceutical field and invite them to become Corporate Members of our Section. They are also starting to plan another Biopharmaceutical Section Membership Survey, which will possibly be targeted for 2001.

Biopharmaceutical Section member stickers are planned for the Joint Statistical Meetings this year, but a new method of distribution needs to be found.

**Assignment:** Phil Pichotta will investigate ways to distribute Biopharmaceutical Section membership stickers at this year's JSM.

**Assignment:** Phil Pichotta will write a paragraph for the AMSTAT News column commemorating the Section's membership exceeding 2000 people.

### ASA Fellows Committee Report

Larry Gould sent out the endorsing letters as Chair of the Biopharmaceutical Section's Fellows Committee, rather than going to the Section Chair for approval, and having the endorsement come from him.

The Fellows Committee received 3 nominations. Two of the three got the Section's endorsement: One was a very strong candidate, one had reasonable justification. One was for someone who had very little to do with the section so was not endorsed.

Discussion ensued about how to protect confidentiality (especially with respect to those candidates who do not get elected fellows). We need to come up with a procedure for the future. It was proposed that at the August meeting the Chair of Fellows Committee present both the people who got elected and who we endorsed. It was decided that we

should discuss the confidentiality issue at the August meeting and also come up with rotation procedure for the Fellows Committee.

**Assignment:** Steve Snapinn will put both the Fellows Committee confidentiality issue and the discussion of Fellows Committee rotation on the agenda.

## PhRMA

The 1999 PhRMA Biostatistics/Data Management Workshop will be held on November 7-10 in Bethesda, MD. The theme will be Benefit/Risk Management, and the Keynote Speaker will be Janet Woodcock.

## Midwest Biopharmaceutical Workshop

Frank Shen reported on the upcoming Midwest Biopharmaceutical Workshop and distributed the final program. The Workshop has an upper limit of 200 participants. This year's program has an emphasis on genomics.

The Workshop would like to use a credit card for registrations. Frank Shen asked whether the Section could help. The Executive Committee didn't feel this to be appropriate without having more information, and Bob Small agreed to pass along some information to Frank Shen that he has on getting Credit Card facilities for a single event like this. Also, Kalyan Ghosh will investigate whether something could be shared with the Deming Conference. This will be discussed further in August.

**Assignment:** Bob Small will provide Frank Shen with whatever Credit Card service information that he has.

**Assignment:** Kalyan Ghosh will investigate whether the Midwest Biopharmaceutical Workshop could share credit card facilities with the Deming Conference.

**Assignment:** Steve Snapinn will include the Section involvement in obtaining Credit Card facilities for the Midwest Biopharmaceutical Workshop as an agenda item for the August Executive Committee Meeting.

## Atlantic City (Deming) Conference

Kalyan Ghosh reported on the 1998 Deming Conference, as well as on the plans for the 1999 Conference.

The 1998 Deming Conference had about 100 people in attendance. The 1999 Conference (12/6/99-12/10/99) will be held at the Resorts Casino Hotel in Atlantic City. The format of the conference will be the same as in previous years.

The program for the 1999 conference is still in the formative stages. So far three seminars have been arranged. Professor Ravi Khattree (Oakland University) will present "An Introduction to the Applied Descriptive Multivariate Analysis Using SAS Software," Professor Dayanand N. Naik, (Old Dominion University) will present "Applied Multivariate Statistical Analysis with SAS Software," and Professor Chap T. Le will present "Applied Categorical Data Analysis." The remainder of the program should be finalized shortly.

Kalyan Ghosh asked whether the ASA Biopharmaceutical Section would be interested in taking over the conference from the ASQC. He felt that the topics are more in line with the Biopharmaceutical Section and that the conference could then get a better location and/or be held at a better

time. The Conference currently makes money, but the attendance is low.

**Assignment:** Kalyan Ghosh will present a formal proposal for the Section to take over the Conference at the August Executive Committee meeting, with the necessary information being distributed prior to August. In particular, Executive Committee members need to know the geographic breakdown of the Conference attendees, where attendees come from, etc.

## Council of Sections Report

Chuck Davis reported on the follow-up correspondence he had received from Walter Piegorsch, Vice Chair of the ASA Council of Sections with respect to the Section's comments on the Strategic Planning initiative.

With respect to mailing of the Section's publications, the Board agreed with that concern, but saw that as a computer system issue ("ongoing problem-solving") and not related to Strategic Planning.

The Executive Committee's other query was for clarification of the ASA policy on publication of papers in Proceedings that were not presented in section-sponsored sessions. Walter Piegorsch's response stated:

"The policy as the Council understands and approves it (and as the Committee on Meetings institutes) is that the primary sponsor of a session has the responsibility of informing contributed (and invited) authors of the opportunity to publish their contributions in that section's proceedings each year. This policy is held steadfast by the ASA publications staff, with no exceptions.

However, if the session's primary sponsor doesn't publish a proceedings, the contributor may elect to contact any of the session's secondary sponsors (if there are any) and request inclusion in their proceedings (if they publish such). That section's publication office (or other such individual) must then contact ASA and give clearance for the appropriate contribution to appear in those proceedings. (One caveat: if the contributor originally submitted his/her abstract to a primary-sponsor section that publishes a proceedings, but later had the abstract moved—with his/her permission—to a primary sponsor that does not publish proceedings, the contributor may request that his/her paper appear in the original sponsor's proceedings (if such exist).")

Since our Section membership is now over 2000 members, it was brought up that perhaps we are now entitled to a third Council of Sections Representative.

**Assignment:** Nancy Smith will check on whether or not we are entitled to a third COS Representative.

## 1999 Joint Statistical Meetings: Invited & Contributed Paper Sessions & Short Courses

Christy Chuang-Stein reported that the Biopharmaceutical Section is sponsoring 3 invited paper sessions at the 1999 JSM. They are "Future Developments in Medical Statistics and Statisticians" organized by Larry Gould, "A Report on the Activities of the Adverse Events Working

Groups" organized by Noel Mohberg, and "Sample Size Estimation in Clinical Trial" organized by Phil Pichotta.

Our Section will sponsor two 1-day short courses. The first one is on "Design and Analysis of Clinical Trials" by Jenpei Liu and Shein-Chung Chow. The second one is on "What They Never Taught You in Graduate School: Dealing with the peculiarities of clinical data in drug studies and their effect upon standard statistical tests and methods of estimation" by David Salsburg. In addition, our Section will co-sponsor a short course titled "Designing and Implementing Economic Evaluations in Health Care" by Joseph Heyse.

Also at the 1999 JSM, our Section will repeat the half-day workshop titled "An Overview of the Role of the Biopharmaceutical Statistician" by Bruce Rodda and Robert Starbuck.

Our Section is sponsoring the following 8 Special Contributed Paper (Topic) Sessions:

- The application of meta-analysis to the regulated medical products (Hollington TC Lu, CBER, FDA)
- Dose proportionality and linear pharmacokinetics (Thomas Bradstreet, Merck)
- Multiplicity issues in randomized controlled trials (Rajagopalan Srinivasan, FDA)
- Designed flexibility in clinical trials (George Chi, FDA)
- The use of modeling and simulation to optimize trial and development strategies for dose finding (Hung-ir Li, Lilly)
- Design and analysis of pharmacokinetic and pharmacodynamic studies (William R. Greco, Roswell Park Cancer Institute)
- Hypothesis testing and multiplicity in clinical trials (Abdul J. Sankoh, Genetics Institute)
- Equivalence testing: FDA perspectives (Tie-Hua Ng, FDA)

In addition, our Section is sponsoring 12 Regular Contributed Paper sessions. Also, nine regular and 2 invited posters have been submitted to the JSM, selecting the Biopharmaceutical Section as the sponsoring section.

We thus have a record year of submissions. The favorable meeting location has greatly contributed to the increase in the number of overall papers. However, our Section's increase is at a rate higher than the overall rate increase.

We would like more applicants for invited paper sessions.

**Assignment:** Tom Capizzi will write an article for publication in the Biopharmaceutical Report by September/October giving suggestions for organizing invited & special contributed paper sessions.

### 1999 Joint Statistical Meetings: Roundtable Luncheons

The Biopharmaceutical Section Roundtable Luncheons will be held on Monday of the JSM. We are sponsoring the following 10 Roundtable discussions:

- (1) Paul Gallo, Novartis, "Center Weighting Issues in the Analysis of Multicenter Clinical Trials"
- (2) Robert Kohberger, Wyeth-Ayerst, "Use of Surrogate Markers in Clinical Trials"

- (3) Ersen Arseven, Arseven Consulting, "Have You Developed the Skills Necessary for your Success in the Pharmaceutical Industry?"
- (4) Imogene Grimes, Pfizer, "The Impact of ICH Guidelines on Protocol Development"
- (5) Vance Berger, FDA, "Discussion of Permutation Tests"
- (6) Ilsoon Yang, Schering-Plough, "Multiplicity Issues in Quality of Life Analyses"
- (7) Keith Soper, Merck, "Alternative Carcinogenicity Tests Using Transgenic or Neonatal Rodents"
- (8) George Chi, FDA, "Demands for Flexibility in Clinical Trials Require Innovative Approaches"
- (9) John Andersen, Eli Lilly, "Statisticians Role in Corporate Decision Making"
- (10) Kathleen Lamborn, University of California, San Francisco, "Clinical Trial Design for Regulatory Approval for Cancer Therapies - Issues and Opportunities"

### 1999 Joint Statistical Meetings: Best Presentation Awards

**Assignment:** Sandy Heft will send the award list to the ASA office in April.

**Assignment:** Lukas Makris will send an announcement to the Biopharmaceutical mailing list.

### 1999 Joint Statistical Meetings: Best Student Paper Awards

Demissie Alemayehu provided an update on the 1999 Best Student Paper Awards contest. The following individuals have volunteered to review papers: Naitee Ting, Sanat Sarkar, Tuli Cnaan, and Demissie Alemayehu. Up to 5 awards will be granted.

Last year there were 12 papers received. To be considered for an award, the student must meet the ASA deadline for abstract submission (2/1/99) and the abstract, manuscript, and endorsement from the student's advisor or department head must be submitted to Christy Chuang-Stein by 5/1/99.

### Program for 2000 ENAR & JSM

Bob Small is starting to work on both the 2000 ENAR and JSM programs. Submissions for Invited Paper sessions for the 2000 JSM are due to ASA in October. Bob Small needs to receive ideas for sessions in August.

### 1999 Joint Biopharmaceutical Section/FDA Workshop

Nancy Smith updated the Executive Committee on the 1999 Joint Biopharmaceutical Section/FDA Workshop. It is entitled, "Theme Statistical Issues for the New Millennium" and will be held on Sept 30-Oct 1 at the Hyatt in Crystal City, Virginia. Approximately 75% of the speakers and session chairs have been identified. The committee is actively looking for industry co-chairs. The Section will allocate our annually allotted AMSTAT News page to the Workshop.

The policy for travel was discussed. In general there is no reimbursement for travel. This needs to be discussed more thoroughly.

### Candidates for Section Officers

This year we will need to elect the following officers: Chair-Elect, Program Chair-Elect, and 1 Council of Sections Representative.

Any suggestions for nominations for officers should be given to Ken Koury. The proposed slate needs to be done by August. Candidates should be solicited from Section members via the electronic mailing list, the web site, and the volunteer list.

### Update to Operations Manual

**Assignment:** All Executive Committee members should review the Operations Manual for necessary updates for discussion at the August meeting. Steve Snapinn will send out a reminder about 1 month before the meeting.

The Operations Manual is on the website.

### Program Committee Proposal

**Assignment:** Steve Snapinn and Tom Capizzi will bring a proposal to the August meeting re establishing a Program Committee.

### Financial Support for Speakers at ENAR & JSM

This year we gave financial support (paid registrations) for 2 invited speakers at ENAR & JSM. These decisions needed to be made at very short notice. Although the Executive Committee supported the decisions, it was decided that requests for funding needed to be submitted well ahead of the registration deadline for speakers; only speakers who are not ASA members and non-statisticians are eligible for reimbursement. Requests must be submitted 1 month in advance and are limited in number. Requests will be approved at the Program Chair's discretion.

## Minutes of ASA Biopharmaceutical Section

### *Executive Committee Meeting*

*August 10, 1999, Baltimore, MD*

#### **Attendees:**

Demissie Alemayehu	Sally Greenberg	Denise Roe
Ersen Arseven	Sandy Heft	Bob Small
Tom Capizzi	Ken Koury	Nancy Smith
Christy Chuang-Stein	Lukas Makris	Steve Snapinn
Avital Cnaan	Jeff Meeker	Keith Soper
Chuck Davis	Anne Meibohm	Naitee Ting
Kalyan Ghosh	Phil Pichotta	Lianng Yuh

### Election Results

Steve Snapinn announced the 2000 election results for the Section:

Chair-Elect: Jeff Meeker

Program Chair-Elect: Keith Soper

Council of Sections Representative (2000–02): Ralph Harkins

In addition, Steve also announced the following election results for ASA:

Chair-Elect, Council of Chapters: Jeff Meeker

District 1 Vice-Chair of Council of Chapters: Frank Shen

Vice-President of ASA (2000–02): George Williams

Ken Koury received official notification from the ASA office that we will get a third Council of Sections Representative beginning with the next election since our membership now exceeds 2000.

### Minutes from the March 29, 1999 Meeting

The minutes of the March 29, 1999 Executive Committee meeting held at the ENAR meetings in Atlanta, Georgia were accepted with a few minor corrections.

### Treasurer's Report

Sally Greenberg reviewed the financial statement for 1/1/99 through 6/30/99 from ASA. There are a few expenses incorrectly categorized and a few which need to be sorted out with the ASA office. Sally will follow up on these. The following bills don't appear in the financial report: (1) room/food for the 1998 Executive Committee Meeting at the ENAR Meetings, (2) 1998 poster donation, (3) bills for the Section's Internet account.

Sally reviewed the actual vs. projected expenses. Since most of the Section's expenses occur at or around the JSM and the fall workshop, it was decided that a more reasonable assessment could be made at the Transition meeting.

It was announced at the meeting of Section Chairs & Treasurers on August 8, 1999 that there will be no preliminary budgets for 2000. Final budgets are due to the ASA office on September 30, 1999. However, Steve Porzio stated that, because of the timing of our Transition meeting, it would be acceptable to finalize the budget by the end of October.

**Assignment:** Sally Greenberg will contact Steve Porzio to:

(1) Resolve phone charges in the 6/30/99 statement from the ASA office.

(2) Move membership printing and postage expenditures from the Biopharmaceutical Report account to the General printing and postage accounts.

(3) Follow up on missing past expenditures with Steve Porzio.

**Assignment:** Sally Greenberg will prepare a draft 2000 Section budget for approval at the Transition Meeting.

### Review of the 1999 Joint Statistical Meetings

#### **Invited and Contributed Paper Sessions:**

Christy Chuang-Stein reviewed the invited and contributed paper sessions of the 1999 JSM. The Section had a banner year with 3 invited paper sessions, 8 special con-

tributed paper sessions, and 12 regular contributed paper sessions.

The Invited Paper Sessions were on the following topics:

- Future developments in medical statistics and statisticians
- A report on the activities of the adverse events working group
- Sample size estimation in clinical trials

Most of the sessions covered clinical statistics topics.

#### **Short Courses & Workshops:**

Christy Chuang-Stein reported that the Section sponsored 3 Short Courses and 1 Workshop at the JSM, on the following topics:

- Designing and Implementing Economic Evaluations in Health Care
- Design and Analysis of Clinical Trials
- Clinical Data and Statistics: What They Never Taught You in School
- An Overview of the Role of the Biopharmaceutical Statisticians (workshop)

Steve Snapinn indicated that registration was low for the "Designing and Implementing Economic Evaluations in Health Care" course, but that it didn't lose money; there were slightly over 20 participants. The "Design and Analysis of Clinical Trials" class registration was around 35 people.

Sandy Heft discussed the Section's Roundtable Luncheons. They were held on Monday at noon. Nine took place, and one was cancelled. All nine went very well, and there were only a few empty seats.

#### **1998 Best Presentation Awards:**

Sandy Heft announced the results of the 1998 Best Presentation Awards. First place went to Catherine Tangen (University of Washington), second place went to Devan Mehrotra (Merck), and third place went to Kristen Meier (FDA).

#### **1999 Best Presentation Awards:**

Lukas Makris discussed the planning for the 1999 Best Presentation Awards. The Session Chairs were instructed to pass out the forms. There are almost 120 speakers who are eligible.

### **Section Business Meeting**

Steve Snapinn reported that for the business meeting and mixer this evening, a common bar would be used for 4 mixers (including ours), with a total of 2 bartenders. ASA was doing this to save money on bartending expenses. Unfortunately, we're the only mixer with an open bar. In order to keep an open bar, we will be handing out coupons to people as they come to the business meeting. We've ordered 500 coupons.

Some discussion ensued as to the best way to handle this. Executive Committee members considered the situation to be awkward no matter how it was handled. The procedure for this evening's Business Meeting was resolved as follows: Four people volunteered to hand out the coupons: Nancy Smith, Sally Greenberg, Sandy Heft, and Ken Koury. There will not be a sign-in at the door; people will only sign in once the business meeting actually starts.

**Assignment:** Steve Snapinn will write a letter to Lee Decker to inform her that we need input into decisions such as sharing of bartenders across mixers that affect our business meeting.

Steve Snapinn reviewed a tentative agenda and solicited further agenda items for the Business meeting.

A discussion occurred as to how to get the word to members about Section activities such as the Business Meeting and Mixer. It was decided that we should set up a Section email mailing list.

**Assignment:** Phil Pichotta will try to obtain an electronic file of section member e-mail addresses from the ASA office.

**Assignment:** Sally Greenberg will set up an announcement type electronic mailing list for all section members based on the list Phil Pichotta obtains.

### **Publications and Proceedings**

Denise Roe gave the Publications Committee report. AMSTAT News articles for 1999 were/are as follows. This rotation will also be used for 2000. The people responsible in 1999 are indicated in parentheses.

- January, 1999: 1998 Section Highlights (Kenneth Koury)
- February, 1999: Member Benefits (Philip Pichotta)
- March, 1999: Biopharmaceutical sessions at ENAR Meeting and preview of Joint Statistical Meetings (Christy Chuang-Stein)
- April, 1999: Biopharmaceutical Report (Anne Meibohm)
- May, 1999: Electronic mailing list (Sally Greenberg) and web site (Kalyan Ghosh)
- June, 1999: 1999 Joint Statistical Meetings Overview (Christy Chuang-Stein) and Biopharmaceutical Section/FDA Fall Workshop (Ralph Harkins) – Did not appear due to problems in the ASA office (a snafu with their computer system). ASA has assured us that future submissions will be included.
- July, 1999: 1999 Joint Statistical Meeting Activities (Christy Chuang-Stein)
- August/September, 1999: Winners of 1999 Best Student Paper Competition (Naitee Ting)
- October, 1999: Executive and Business Meeting Summary from Joint Statistical Meetings (Sally Greenberg)
- November, 1999: Student Paper Competition Procedures (Naitee Ting)
- December, 1999: Summary of Fall Workshop (Ralph Harkins)

Individuals should send AMSTAT News articles to Denise Roe, who will forward them to ASA. Suggestions for additional topics should be given to Denise.

The 1998 Proceedings are being printed. We agreed with the ASA recommendations for press size and publication prices (\$30). The deadline for submissions for the 1999 proceedings is mid-October. Individuals should let Denise Roe know if other meetings cosponsored by the section will be submitting papers. Speakers from the 1999 Muncie meetings have already been invited to publish in the Proceedings.

There was some discussion as to whether it is required to pay page charges in order to publish a paper in the Proceedings.

**Assignment:** Denise Roe will get the rules on page charges for Proceedings clarified.

Some individuals received copies of the 1997 Proceedings rather than 1998 ones. The ASA office sent correct copies by Federal Express after members complained.

### Council of Sections Report

Chuck Davis reported on the Council of Sections meeting. The Strategic Planning Initiative allotted \$100,000 in 1999 in support of:

1. Enhancing the impact and health of our discipline
2. Supporting professional statisticians
3. Developing and nurturing an efficient organization that will continue next year with an additional \$100,000

Any ideas should be provided to Steve Snapinn.

The ASA Archives Committee would like each section to compile a section history.

Online activities are being furthered with the appointment of Brian Yardell as the Editor of AMSTAT online. He has 10 Associate Editors. Tom Devlin is the Associate Editor for Sections.

The Board of Directors has approved Ethical Guidelines for Statistical Practice; these are available on the web. The new ASA membership directory and CD were mailed last week; all members will receive both. Full membership dues are increasing from \$74 to \$80. A section on Nonparametric Statistics was approved. A Committee on Electronic Communications was formed.

It was proposed at the Council of Sections meeting that sections who having members who review papers in non-statistical journals should consider notifying Ray Waller of the names of the members and the journals in order for the ASA to send out "thank you letters" to the journals. The Biopharmaceutical Section Executive Committee considered this to be patronizing, although fully in agreement with the sentiment.

Brian Yardell wanted to know which sections are interested in Electronic Proceedings.

**Assignment:** At Thursday's COS Debriefing, Nancy Smith should recommend to the Council of Sections that they encourage journals to use statistical reviewers more, rather than sending "thank you letters" to journals when a statistical reviewer is used.

**Assignment:** At Thursday's COS Debriefing, Nancy will convey the Section's support of electronic proceedings. She will find out the cost, timing, and feasibility for creating an electronic version of back issues. She will convey the Section's desire to be a test case.

### PhRMA

Liannng Yuh reported on PhRMA activities. Proceedings of last year's workshop have been published. Ken Koury is Program Chair for 1999. This year's workshop will be held on November 7-10, 1999 at the Hyatt Regency Hotel in

Bethesda, MD and is entitled "Balancing the Benefits and Risks of Pharmaceutical Products"; the Keynote Address will be given by Dr. Janet Woodcock.

**Assignment:** Ken Koury will publish an article summarizing the fall PhRMA workshop in the last 1999 issue of the Biopharmaceutical Report.

Post-Meeting Note: The deadline for articles to be submitted for the last 1999 issue is now scheduled for November 14th, so the specific issue needs to be clarified.

### Biopharmaceutical Report

Ersen Arseven provided an update of Biopharmaceutical Report activities. It had been planned to publish 3 issues in 1999. The Spring 1999 issue has been published, and the Summer 1999 issue was finalized recently. It is expected that the Summer 1999 issue will be mailed out by the end of August or early September. The goal is to publish and distribute the Fall/Winter 1999 issue by the end of 1999; contributors to this issue have been given timelines in accordance with this goal.

It was recommended that all past issues of the Biopharmaceutical Report be made available on the Section's website, perhaps scanned in and posted as Adobe Acrobat (PDF) files.

The Biopharmaceutical Report will publish a list of Fellows elected from the Section, along with citations.

### Electronic Mailing List

Sally Greenberg reported on the Section's electronic mailing list. Subscriptions to the mailing list continue to grow, with membership now totaling 146 people.

Sally is looking for a few volunteers who are willing to be responsible for monitoring the list when both she and David Carlin are unavailable for more than a day or two. All that these people would need to do is to unsubscribe people who create infinite loops (although they would actually have full moderator privileges). Currently Phil Pichotta has that power, as well as Sally Greenberg and David Carlin. Both Anne Meibohm and Christy Chuang-Stein volunteered.

### Web Site

Kalyan Ghosh reported on the Section's web site. After discussion by the Executive Committee, it was decided that Kalyan should add links to non-Section sponsored conferences if they are submitted to him (i.e., he shouldn't be expected to seek them out). It was also decided that draft programs of Section-sponsored workshops and meetings should be added to the website if available.

**Assignment:** Kalyan Ghosh will add web site links to relevant non-Section sponsored conferences that are submitted to the Section.

**Assignment:** Kalyan Ghosh will add draft programs (or links for draft programs) for Section-sponsored workshops/conferences to the website if/when they are available.

### Midwest Biopharmaceutical Workshop

Frank Shen submitted a report on the Midwest Biopharmaceutical Workshop. This year's workshop had record attendance (216). Genomics was a main theme. There were

2 plenary sessions, 1 tutorial, 4 clinical sessions, and 5 non-clinical sessions, all of which were well attended. Tentative dates for 2000 are May 22-24. Ken Gerald from Applied Logic Inc. (kgerald@alogic.com) will chair the workshop for 2000. Stacy David from Eli Lilly is the clinical co-chair, and Mike Lutz (GW) and Jim Colaianne (J&J) are the non-clinical co-chairs. Any suggestions should be forwarded to Ken Gerald.

At the previous meeting it was proposed that the Midwest Biopharmaceutical Workshop explore sharing of credit card facilities with the Atlantic City conference. Kalyan Ghosh reported that the Atlantic City Conference can use the ASQC's credit card facilities if desired, so have no financial reason for sharing additional costs with the Muncie workshop.

### Atlantic City Conference

Kalyan Ghosh reported on the Applied Statistics Conference. The conference made \$25,000-\$30,000, so the ASQC wants to continue to sponsor it.

### 1999 Joint Biopharmaceutical Section/FDA Workshop

Nancy Smith reported on the progress of the 1999 Joint Biopharmaceutical Section/ FDASA Workshop. The program/registration flyers are now available; copies are at the JSM. We will have a larger room than last year.

There was some discussion as to what our profit-sharing agreement is with ASA, i.e., whether ASA takes the first \$5000 and we take 100% after that OR whether there's a 50/50 split.

**Post-Meeting Note:** The 1998 budget shows a 50/50 split.

### 2000 Program for ENAR & JSM

Bob Small reported on the 2000 programs for the ENAR meetings and the JSM. We have 2 invited sessions for ENAR. ENAR was not aware that we are a cosponsor. Every year has different problems with invited paper session allocation and timing, and the Biopharmaceutical Section Program Chair starts from scratch every year.

**Assignment:** Steve Snapinn will write a letter to next year's president of ENAR to improve coordination of the program committee of ENAR with the Program Chair of the Biopharmaceutical Section and to reiterate that the Biopharmaceutical Section, as a co-sponsor, is expecting to have invited paper sessions at the Spring meeting. This will include a discussion of previous correspondence.

**Assignment:** Keith Soper will contact next year's ENAR Program Chair as soon as possible to work out the invited paper sessions for the Spring Meeting.

We have 4 Invited Paper sessions for the 2000 JSM. Only 4 sessions are in the competition for next year.

### ASA Fellows Committee Report

Larry Gould provided an update on the Fellowship Committee's activities. The willingness and procedure for the Fellows Committee to review and support Fellows nominations on behalf of the Section has now been publi-

cized at the 1998 JSM, in the newsletter, and on the website. The Fellows Committee does not put packages together; this is something that the initiator needs to do. A new member is needed on the Fellows Committee so that someone can rotate off.

Three more or less complete nomination packages were received this year. The Committee reviewed all three and agreed to support two. The Fellows Committee feels that it is important that Section support not be merely a rubber stamp. Formal letters of support from the Section were added to the nomination packages of the two candidates. The Fellows Committee feels that confidentiality protection is optimal as procedures currently stand.

Results of the Fellows elections are not completely known at present. Consequently, it is not known how many nominations of Section members were submitted beyond the three sent to the Section's Fellows Committee.

### 1999 Best Student Paper Awards

Naitee Ting discussed the results of this year's Biopharmaceutical Section Student Paper Awards Competition. The award consists of a certificate and a cash award of \$1,000. The four winners were:

1. Andrew S. Allen—*General Marginal Regression Models for the Joint Modeling of Event Frequency and Correlated Severities with Applications to Clinical Trials*
2. Tomasz Burzykowski—*Validation of Surrogate Endpoints in Multiple Randomized Clinical Trials with Failure-Time Endpoint*
3. Radha A. Railkar—*A Simultaneous Testing Strategy for Comparing Two Treatments in a Stratified Binomial Trial*
4. Shenghui Tang—*Analysis of Longitudinal Data with Informative Competing Causes of Dropout*

The student paper reviewers for this past year were Demissie Alemayehu, Thomas Bradstreet, Avital Cnaan, and Naitee Ting (Chair). The papers were sent to committee members on May 17 with author names and addresses removed from the cover pages. Committee members reviewed all papers following the established criteria. The four winners were chosen based on scores from all 4 reviewers.

The committee discussed the promotion and review process and made the following recommendations:

- Committee members should have a teleconference before evaluating the papers so that they can establish some common understanding.
- We should increase advertising:
  - Send announcements to individual professors, instead of departments in general
  - Focus on professors who are also Biopharmaceutical Section members
  - Send a follow up notice and another AMSTAT NEWS announcement in February or March
  - Announce in "The Stats" journal.
- In the announcement, we should be clear of the 4 categories for evaluation, and be specific as to what will satisfy these categories.
- We should limit the papers to students who are either the single author, or the primary author (i.e., not

allowing the student's name to appear after their advisor's name).

- The Section should continue to recommend 3 members for the committee with a 3-year term for each member on a rotating basis. Demissie Alemayehu (2 years) and Thomas Bradstreet (1 year) have interest in continuing to serve in the committee, and Naitee Ting will rotate off the committee. We recommend the Executive Committee to name a chair and a new member before next April.

### Membership Committee

Phil Pichotta gave the Membership Committee report. The Section had 2064 individual members and 4 corporate members as of May 1999. A new Biopharmaceutical Section membership brochure is now available. The membership listing is now available on the Section's website.

Other accomplishments included:

- Preparing stickers of our Section logo
- Providing a letter and sending a broadcast message to Section members at JSM that invited them to the Business meeting and mixer and which listed Invited and Special Contributed Sessions at the Meeting.

The Fellows Committee still needs an electronic file/listing of Fellows of the section.

**Assignment:** Phil Pichotta will submit a request to Mary Fleming at the ASA office to get an electronic copy of the information required by the Biopharmaceutical Section Fellows Committee.

### Candidates for Section Officers

Ken Koury needs to get nominations to ASA by the end of September for the following officers for 2001:

- Chair-Elect
- Program Chair-Elect
- Publications Officer
- New Council of Sections Representative

Please contact Ken Koury with any names for consideration.

### Executive Committee Appointments

Tom Capizzi reported that two Executive Committee positions need to be filled for 2000. Other appointments that need to be made include Associate Editor of the Biopharmaceutical Report, Chair of the Membership Committee, Chair of the Student Paper Awards Committee, and Roundtable Luncheon Coordinator. For the last position, appointment of an existing executive committee member is desired.

### Miscellaneous

**Assignment:** All Executive Committee members should review both the Biopharmaceutical Section Charter and the Biopharmaceutical Section Manual of Operations prior to the Transition Meeting.

## Congratulations 1999 ASA Fellows!

Congratulations to the members of the Biopharmaceutical Section who were elected as Fellows in 1999! The new fellows and their citations are:

**Roger L. Berger**, Professor, Department of Statistics, North Carolina State University: For research contributions in the areas of hypothesis testing, contingency tables, and bioequivalence; for excellence in teaching through textbook authorship; and for service to the profession.

**Mei-Ling Ting Lee**, Assistant Professor, Harvard Medical School, Harvard University: For influential contributions in statistical applications in microbiology and medical research; for pioneering editorial work; for contributions to the theory and application of association of multivariate distributions; and for service to the profession.

**Joseph W. McKean**, Professor, Department of Mathematics and Statistics, Western Michigan University: For many contributions to nonparametric and robust statistics, particularly in rank-based methods; for dissemination of these advancements to the wider community of practitioners; and for outstanding editorial service.

**Keith A. Soper**, Statistical Scientist, Merck Research Laboratories: For excellence in the application of statistical methods to the design and analysis of preclinical drug safety studies, and statistical research in cytogenetics; for promotion of practical solutions for multiplicity in safety assessment; and for service to the profession.

**Roy N. Tamura**, Senior Research Scientist, Eli Lilly and Company: For research in biopharmaceutical methods; for improving communication between industry and academic statisticians; and for statistical leadership in the pharmaceutical industry.

## FOURTH ANNUAL FDA-INDUSTRY WORKSHOP: STATISTICAL ISSUES FOR THE NEW MILLENNIUM

Ralph Harkins

The annual FDA/Industry Workshop, which is cosponsored by the ASA Biopharmaceutical Section and the Food and Drug Administration Statistical Association (FDASA), was held at the Hyatt Regency in Arlington, Virginia from September 30-October 1, 1999. As the fourth in this series, this workshop continues to stress the mutual industry and FDA philosophy of providing a cooperative grass-root level forum for open dialog, discussion and exchange of ideas, problems and possible solutions relating to drug and device development as well as discussions of the statistical/regulatory impact of ICH, PDUFA, FDAMA and related topics of interest to our membership.

Evaluations submitted by the approximately 286 attendees again rated the workshop as highly successful. These evaluations are very important since they provide direction and information to the Biopharmaceutical Section Executive Committee in planning and scheduling this workshop. Suggestions were solicited for future workshops and there are two suggestions currently under consideration. The first is to plan luncheon round-table discussions for topics of interest to a limited number of our members. The second suggestion is to allow recruiters to ply their trade officially during the workshop. The latter suggestion does not seem to be in consonance with the Biopharmaceutical Section's goals and philosophy for the workshop. However with over 2,000 members recruiters have noticed our workshop. We are interested in your input and comments regarding whether to implement either of these suggestions.

Attendee's evaluations last year indicated many members were interested in general, broad based drug and device development issues as well as topics related to the specific Biologic, Device/Diagnostic or Drug Development FDA Centers. In view of this interest and the growth and success of this workshop, the number of sessions was increased to accommodate these interests. Simultaneous sessions relating to specific FDA Centers were held on Friday morning. This allowed an increase from six sessions discussing statistical issues last year to 10 sessions this year. The format established a few years ago of one speaker each from FDA, Industry and Academia for each session was generally followed. Some sessions included a discussant or panel of discussants. Every effort was made to provide time for attendees to ask questions and foster open discussion of materials presented.

The Program Committee can certainly be thanked for their generous contribution of time and thought to the success in organizing this workshop. The Co-Chairs for this year's workshop were Nancy Smith of FDA and Ralph Harkins of Quintiles. Representing FDA on the Committee

were Chuck Anello, Bob O'Neill, Nancy Smith, Greg Campbell, Anna Nevius, Harry Bushar, and Henry Hsu. Ji Zhang, (Merck and Co., Inc.), Robert Small, (Pfizer), Lukas Makris, (BioCor), Sandy Heft, (Schering Plough), Tony Segreti, (Glaxo Wellcome) and Ralph Harkins, (Quintiles) represented industry. However, the committee's time and effort would certainly have gone for naught had it not been for the excellent work of the session Chairs and the speakers who devoted so much time and energy to their sessions and presentations.

The opening session was devoted to members of FDA management updating attendees on developments and initiatives that impact statistical/regulatory relationships. Dr. R. O'Neill (CDER), Dr. A. Lachenbruch (CBER), Dr. G. Campbell (CDRH) and Dr. A. Nevis (CVM) presented their respective center's position in "The Role of Statistics in our Changing Regulatory Environment".

The sessions covered the following topics: "Interim Analysis and Data Safety Monitoring Boards", "Meta Analysis Applied to Non-Inferiority Trials", "Multiple Locations, Inference Space, Mixed Models, and their Impact on Design and Analysis of Experiments", "Use and Misuse of Covariance Analysis in Clinical Trials", "Statistical Issues in Diagnostic Medical Products", "Statistical Interpretive Issues in Health Related Quality of Life Data", "Some Approaches to Post-marketing Surveillance Safety Assessment", "Perspectives in the Use of Bayesian Statistics in Clinical Trials", "The Design and Analysis of Studies to Assess the Effect of Inhaled Steroids on Growth" and "Issues in the Analysis of Data with Missing Values". Speakers were approximately evenly distributed among government agencies, industry and academia.

There was a mixer on the evening of the first day of the workshop that gave all an opportunity to renew old friendships and make new ones as well as giving members the chance to exchange ideas with industry, academic and government colleagues.

The Biopharmaceutical Section Executive Committee has decided to sponsor another Workshop next year. The year 2000 Co-Chairs are Greg Campbell of FDA and Sandy Heft of Schering Plough. Be sure to get your ideas and wishes to your Committee early in year 2000 so that they can be considered for the Year 2000 workshop.

# THE 23rd ANNUAL MIDWEST BIOPHARMACEUTICAL STATISTICS WORKSHOP

MAY 22–24, 2000 • BALL STATE UNIVERSITY • MUNCIE, INDIANA

## Preliminary Program

### MONDAY, MAY 22

#### \*\*NEW FEATURE\*\*

9:00 a.m.–12:00 p.m. **SHORT COURSE** (Fee Event)  
Presenter: Charles Davis, U of Iowa, "Mixed Modeling, with Emphasis on Proc Mixed"

2:30 p.m.–2:45 p.m. **INTRODUCTION AND WELCOME**  
Ken Gerald, Applied Logic Associates, Representative from Ball State University

2:45 p.m.–6:15 p.m. **PLENARY SESSION**  
Speaker: LEMUEL MOYE, University of Texas Health Sciences Center, "Conducting Multinational Clinical Trials"

### TUESDAY, MAY 23

8:30 a.m.–11:30 a.m. **CONCURRENT SESSIONS**

A. Sample Size Re-estimation—Cardinal Hall B

Organizer/Chair: M. Birkett, Eli Lilly and Co.

1. "Sample Size Redetermination for Repeated Measures Studies," J. Denne, De Montfort U.
2. "Sample Size Re-estimation: Recent Developments and Practical Considerations," L. Gould, Merck Research Laboratories.
3. "Some Practical Experiences with Sample Size Recalculation," J. Wittes, Statistics Collaborative.

B. Computer Assisted Modeling and Simulation of Clinical Trials—SC 301-302

Organizer/Chair: J. Natarajan, R.W. Johnson PRI.

1. "The Usage of Modeling and Clinical Trial Simulation in Early Clinical Development", H.-I. Li, Eli Lilly and Co.
2. "Application of Clinical Trial Simulation for a Crossover Study for Alzheimer's Disease," P. Lockwood, Parke-Davis.
3. "Experiences with Clinical Trial Simulations - Lessons Learned" -Panel Discussion, H.-I. Li, Eli Lilly; P. Lockwood, Parke-Davis; K. Engleman, Astra-Zeneca; S. Liao, R.W. Johnson, PRI; TBA, FDA.

C. High Throughput Screening—FORUM

Organizer/Chair: F. STEWART, Smithkline Becham

1. "A Comprehensive Approach for Gene Expression Analysis from Feature Extraction to Clustering," K. TATSUOKA, Smithkline Becham.
2. "A Model for Assessing Attrition in HTS," F. GAO, Pfizer.
3. "Pattern Recognition and Feature Extraction for Complex HTS Data," F. STEWART, Smithkline Becham.

12:30 p.m.–1:45 p.m. **POSTER SESSION**

Chair: LINDA LEONARD, Pharmacia & Upjohn.

Note: Posters are being accepted on any relevant statistical topic until April 16!

1:45 p.m.–4:45 p.m. **CONCURRENT SESSIONS**

A. Use of Surrogate Endpoints in Medical Research—Cardinal Hall B

Organizer/Chair: M. HOSEYANI, Procter & Gamble Pharmaceuticals

1. "A Statistical Framework for Justifying the Use of Near-term Surrogates for Long-term Outcome," R. Carter, U of Florida.
2. "Statistical Validation of Intermediate Endpoints for Chronic Diseases: Use of Logistic Regression and Non-parametric Bootstrap Method," S. Sarkar, Eli Lilly and Co.
3. "Surrogate Endpoints in Clinical Trials: A Statistical Reviewer's Perspective," N. LI, Division of Biostatistics, CDER, FDA.

### TUESDAY, MAY 23

B. Data Visualization in Biometrics Research—SC 301-302

Organizer: D. Amaratunga, J. Colaianne, R.W. Johnson PRI

Chair: J. Colaianne, R.W. Johnson PRI

1. "Data Visualization using xGobi," D. Swayne, AT&T.
2. "A Visual Look at a Structure Activity Database," D. Amaratunga, R.W. Johnson PRI, and J. Cabrera, Rutgers U.
3. "Investigating Different Layouts and Symbolizations in Studying Gene Expression Data," D. Carr, George Mason U.
4. "A Model Tour for Visualization of Response Surfaces," T. Wang, Merck Research Laboratories.

C. Pharmacogenomics: Crossroads Between Genetic and Clinical Studies—FORUM

Organizer/Chair: F. Shen, Bristol-Myers Squibb

1. "The Role of Statistics in Pharmacogenomics: Differentiating Hope from Hype," F. Shen, Bristol-Myers Squibb.
2. "Genetics Datamining in Clinical Trials," C. Lambert, Golden Helix Datamining, Inc., D. Zaykin and S. S. Young, Glaxo Wellcome, Inc.
3. "Comparison of study designs to detect genetic association," J. Rogus, Harvard School of Public Health

#### BANQUET

Speaker: JANET WITTES, Statistics Collaborative

### WEDNESDAY, MAY 24

8:30 a.m.–11:30 a.m. **CONCURRENT SESSIONS**

A. Bayesian Design and Analysis of Clinical Trials—Cardinal Hall B

Organizer/Chair: M. Gönen, Memorial Sloan-Kettering Cancer Center

1. "A Bayesian Evaluation Of An Improved Chemical Entity," R. SURESH, Schering-Plough Research Institute.
2. "Recent Progress in the Bayesian Approach to Drug Development," D. Berry, MD Anderson Cancer Center.
3. "Bayesian Design and Analysis of Active Control Clinical Trials," R. Simon, NCI.
4. "Issues In Developing Software For Bayesian Planning And Analysis Of Clinical Trials," I. Painter, Talaria, Inc.

B. Gene Expression Research—SC 301-302

Organizer/Chair: K. Ghosh, Bristol-Myers Squibb.

1. "Experimenting and Discovering With Gene Expression Databases," G. Tucker-Kellog, Genetics Institute, American Home Products.
2. "Escape and Noise: Pre-processing Gene Expression Data," N. Siemers and S. Ge, Bristol-Myers Squibb.
3. "Issues in Standardization of DNA Microchips," D. Amaratunga, R.W. Johnson PRI, J. Cabrera, Rutgers University
5. "Molecular Classification of Cancer: Class Discovery and Class Prediction," P. Tamayo, Whitehead Institute, MIT Genome Center.

C. Experimental Design—FORUM

Organizer/Chair: M. LUTZ, Glaxo Wellcome.

1. "Modern Experimental Design Techniques for Biopharmaceutical Research," C.F.J. Wu, U of Michigan.
2. "Uniform Coverage Designs for Drug Discovery," R. Lamm, Glaxo Wellcome.
3. "Training in DOE at Glaxo Wellcome," D. COOPER, Glaxo Wellcome.
4. "Quality Function Deployment as a Planning Tool for Experimental Design," B. EVANS, Glaxo Wellcome.

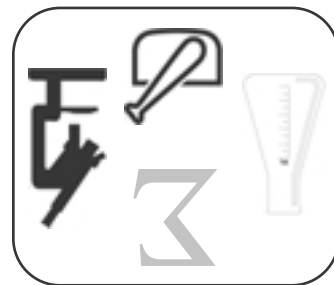
### *Let's Hear from You!*

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