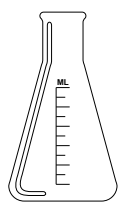


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Opportunities and Challenges for Industry and FDA

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1. Introduction

The Biostatistics Subcommittee of the Pharmaceutical Research and Manufacturers of America (PhRMA) sponsored a workshop on biostatistics and clinical data management on November 9-11, 1998, in Bethesda, Maryland. The theme of the workshop was opportunities and challenges for industry and the Food and Drug Administration (FDA). Liangng Yuh, Senior Director of Biometrics at Pfizer Central Research, served as program chair. The program committee consisted of Tom Copenhaver (Wyeth-Ayerst), Hugh Donovan (Hoechst Marion Roussel), and Kenneth Koury (Schering-Plough). Approximately 145 people, including speakers, attended the workshop.

The purpose of this article is consistent with the purpose of the workshop: to share learnings from and enhanced understanding of multiple perspectives in order to foster collaborations on the future discovery, development, and marketing of medicines to improve health. It is worth mentioning that some sessions have more detail than others, because we could not attend all parallel sessions and relied on our interpretation of the key aspects from the sessions that we attended and from the handouts provided. However, we sought the input and comments from all speakers and chairpersons. We think that this not only helped to ensure accuracy and representation, but also offered the opportunity to summarize those presentations and sessions that we did not attend.

2. Keynote Address

Michael Friedman, Acting Commissioner of the FDA, began his keynote address by noting that five prescription products were recalled by the FDA between September 1997 and June 1998. Two major themes were raised: 1) to examine whether there is a relationship between increased speed of an FDA review and recall of prescription products and 2) to reexamine the post-marketing surveillance system.

Friedman gave an overview of the five products that were recalled by the FDA from September 1997 to June 1998. He noted that critics have claimed that the increased speed in FDA reviews has increased the chance that the FDA missed serious adverse events. The median approval time for a Center for Drug Evaluation and Research (CDER) review has fallen from 27 months in 1992 to 12 months in 1998. Friedman noted, however, that the quality of the reviews has not suffered. The data suggest no relationship between the length of the FDA review and the removal of drugs over the last two decades. *see Industry/FDA, page 2*

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In his conclusion, Friedman mentioned that there will never be enough patients participating in pre-marketing trials to detect the rare events that occurred. The FDA post-marketing surveillance system, which updates the number and type of adverse events, is one way to obtain a complete picture. Another way is for the FDA to link with academic and hospital databases. The data indicate that the five drugs recently recalled do not indicate a failure on part of the FDA system, however.

3. Can We Make Better Use of the Data We Are Collecting?

Kenneth Koury, Director of Statistics at the Schering-Plough Research Institute, chaired this plenary session that focused on the efficiency in reporting clinical data. Unnecessary collection, summarization, and reporting of data consume resources of the sponsor and the FDA. This works against the common objective of accelerating the development and approval of new pharmaceutical products. It is also important to use more fully the data that we do collect.

Efficient Reporting of Clinical Studies

David Fitts, Associate Director of Biometrics at SmithKline Beecham Pharmaceuticals, stated that sponsors should care about efficient reporting. Citing industry trends to control development costs and optimize resource utilization, Fitts characterized clinical data as another industry resource and suggested 'minimal sufficiency' should be the reporting goal. Suggestions to help achieve this included: maintaining an active and explicit focus on prospectively-defined objectives, reporting only results that support experimental conclusions, presenting results in hierarchical fashion with appreciation for the diminishing power of supporting analyses, adopting a strategy for covariate selection (credited to Frank Harrell), and maintaining a consistent philosophy for the exposition of experimental results.

Fitts warned that efforts to achieve efficiency will be met with resistance. Recognizable obstacles to the goal of minimal sufficiency include: intellectual conflict between the quest for knowledge and the limits of clinical data, flexible and broad interpretation of reporting guidelines, fear of failing to address all questions of interest, and the multiple strategic objectives of industry-sponsored research (e.g., regulatory submissions, promotional literature, and manuscripts). Fitts emphasized that planning is the key and proposed a 'backward' development paradigm. He suggested a sequence in which sponsor expectations for a final report should drive preparations of the analysis plan which would define the data required (i.e., the case report form) and ultimately lead to protocol development.

Making Better Use of All the Clinical Studies in an NDA

Charles Anello, Deputy Director in the Office of Biostatistics at CDER, FDA, discussed the impact of the Prescription Drug User Fee Act (PDUFA), the FDA Modernization Act (FDAMA), and the International Conference on Harmonisation (ICH) on New Drug

Application (NDA) review times and the move towards electronic and international submissions. Anello stated both a legal and an ethical basis for the requirement of a full report on all the relevant data in the NDA. A full report would include, among other elements, data from individual studies on which the sponsor would like to base claims of safety, efficacy, and the recommended dose and the collective evidence (contained in the integrated summaries of safety and efficacy). Collective evidence might be useful for safety evaluations and refining estimates of treatment effect (e.g., with regard to age and gender). An analysis plan would address the analysis of the individual studies and the handling of the collective evidence.

Anello also discussed how good review practices can help make better use of the data submitted in the NDA. The goal of the review includes ruling out bias, measuring how likely the result could be expected by chance, and estimating the important clinical treatment effects (both safety and efficacy).

Referring to ICH E3 and E9, Anello discussed several reporting strategies which may be useful. These include presenting all the relevant data, providing good indexing to the NDA, and reporting in a manner that conserves the resources of both the FDA and the sponsor. He encouraged the sponsor to meet with the appropriate medical review division at the FDA prior to submitting the NDA in order to avoid submitting unnecessary data or unnecessary summaries. Finally, to learn more about the year 2002 goal to have a fully electronic submission, Anello provided the FDA Web site (www.fda.gov/cder/guidance) as a source of information.

Optimal Labeling of Clinical Safety Information: Balancing Diverse Customer Needs

Fredric Cohen, Clinical Research Physician from Eli Lilly and Company, presented the results of a telephone survey of 242 physicians. The physicians were classified as being in primary care or obstetrics/gynecology and were chosen randomly among raloxifene prescribers. The results had a 8% margin of error.

Seventy-two percent of the physicians referred to a label before prescribing a new drug for the first time; there was no difference between physicians in primary care and those in obstetrics/gynecology. Physicians of both specialties paid particular attention to contraindications, dosing and administration, and adverse reactions; 48% to 66% referred to at least one of these three sections before prescribing a new drug for the first time. Sixty-one percent of the physicians thought the label provided the right amount of clinical safety information, while about one-third thought the label provided too much of this information. Sixty-two percent found the safety labels useful. Those physicians who referred to safety labels less than 50% of the time before prescribing a new drug for the first time were significantly less likely to feel that these labels were extremely useful (9% vs. 30%) and significantly more likely to feel that there was too much information in them (48% vs. 29%), compared with those who utilized the labels more frequently (p -value < 0.005 for both comparisons). There was no dominant free-form response as to how to improve safety labeling.

Cohen presented the results of a second survey—a sponsor survey—of Lilly employees, who gave specific sugges-

tions on how to improve on labeling. Those surveyed indicated that safety labels should meet prescribers' needs, should cause predictable prescriber behavior, should focus on medical knowledge (rather than legal needs), should be better organized, and should focus on casually related adverse events.

Many issues raised during this presentation were discussed in Working Group III (1995) of the Council for International Organizations of Medical Sciences.

Data Collecting in Phase III

Robert Temple, Associate Director for Medical Policy and Director in the Office of Drug Evaluation I at CDER, FDA, said that there is considerable flexibility on what to report. The most important question, because it could affect the number of people studied, is not what to report but rather what data to collect.

There is tension between the amount of data and the number of patients. "Large simple" (L-S) trials are recognized for their ability to detect modest but important benefits. They also reduce data collection and focus on what's important. By decreasing the amount of baseline data collected, L-S trials limit potential subgroup analysis in one way but enhance it in another by enlarging sample size. A question that could be asked is whether L-S trials should be routine for widely used drugs, giving an order of magnitude more assurance against rare serious events.

With respect to L-S safety and large outcome trials, candidates for reduced data collection include frequent routine lab values, adverse reactions that do not lead to death or discontinuation of therapy, and concomitant medications. Monitoring is a major expense that can be also reduced. The industry standard for monitoring is approximately monthly for all sites. One possibility is to decrease this frequency to every 8 or 12 weeks. Temple also mentioned the potential for cross-study evaluation. As databases become electronic, some potential exists to use them to answer questions. There is no overall FDA policy yet on the topic of this session.

4. Using Innovative Statistical Methodology in Clinical Trials: Real Examples, Policy, and Guidance

Samuel Heft, Senior Director of Statistics at the Schering-Plough Research Institute, chaired this session in which representatives from industry described actual trials where innovative statistical methods have been used. Topics covered in the presentations included the motivation for using the new methods, the development and adaptation of such methods at the protocol and planning stages, the experience gained in applying these methods, and the difficulties encountered in describing the methods to the study team and to regulatory authorities. From the regulatory agency's point of view, difficulties may arise when nonstandard methods are applied; in particular, the appropriateness of the methodology to the clinical setting may not be fully accepted. Moreover, it may not be apparent that the criteria for demonstrating clinical effectiveness are consistent with the criteria previously established for other studies.

Multiple Imputation in Longitudinal Clinical Trials: Implementing a Novel Application in a Regulatory Environment

Moraye Bear, Associate Director of Biostatistics at Amgen, presented the multiple imputation technique and noted that this was the first time that the technique had been used prospectively in a randomized clinical trial setting. The disease under consideration was Amyotrophic Lateral Sclerosis (ALS), known also as Lou Gehrig's Disease, a neurodegenerative disease with a 3 to 5-year median survival time.

Based on the Phase I and II trials, about a 20% dropout rate was anticipated in the longitudinal Phase III study. The primary analysis was based on intention-to-treat. Limitations of the last observation carried forward (LOCF) and the "worst-case" approaches for imputing missing values were discussed. The multiple imputation approach, described in Lavori et al. in *Statistics in Medicine* (14: 1913-1925, 1995), was chosen prospectively as the primary approach. It was selected because it has well-known statistical properties and it was acceptable to the sponsor (Amgen), clinicians, and FDA. Secondary analyses included completers-only analysis, mixed-model analysis, and "worst-case" analysis. The multiple imputation worked well. Agreement existed between the multiple imputation and the secondary (sensitivity) analyses.

Implementing the multiple imputation procedure involves the propensity score method, which uses a logistic regression model, and then grouping patients into quintiles based on their propensity scores. In typical problems, doing the imputation three times works well (Rubin and Schenker, *Statistics in Medicine* 10:585-598, 1991). More research is needed on the propensity model, missing data for baseline scores, and issues surrounding the possible disagreement between the main and sensitivity analyses. Bear suggested that researchers start discussions early, do their homework, get support from clinical colleagues, document rationale, and work through anticipated issues.

An Application of Maximum Likelihood Regression Methods for Paired Binary Data in the Presence of Missing Data

Mei-Hsiu Ling, Manager of Statistics at the Schering-Plough Research Institute, described the Ribavirin Relapse Studies in which Intron plus Placebo was compared against Intron plus Ribavirin in the treatment of Hepatitis C infection. The treatment period was 24 weeks with an additional 24-week follow-up period. A composite endpoint was developed to characterize the patient's overall response to treatment. It was well-recognized that follow-up liver biopsies would not be obtained for all patients. Proportional imputation was originally proposed to estimate the overall response rate in the presence of missing biopsy data. The proportional imputation approach involves the pooling of data from all treatment groups, computing the percentage of improved biopsies among patients with complete data, and assuming the same percentage of improved biopsies among patients with missing biopsies.

After discussion with the FDA, a new methodology was developed to handle appropriately the missing data. This analysis plan was based on the maximum likelihood regres-

sion methods for paired binary data proposed by Lipsitz, Laird, and Harrington in *Statistics in Medicine* (9:1517-1525, 1990). These authors reviewed the proposal and verified that the method was appropriate for the Ribavirin setting and that the underlying assumptions appeared to be justified. Ling provided a detailed description on how this methodology was used in the Ribavirin study. Remaining issues were how to explain the maximum likelihood estimates to non-statisticians (clinicians) and which response rates should be reported in the labeling.

Innovative Statistical Methodology—Some Examples, Suggestions and Guidance

George Chi, Director in the Division of Biometrics I at CDER, FDA, began with a dictionary definition of innovation as “something new or unusual.” He added to it the desirable attributes of being scientifically sound, appropriate from a regulatory perspective, practical from a sponsor’s perspective, and ethical from a patient’s perspective. These qualities are especially appropriate for Phase III studies. He mentioned that an innovation can be an application of a known method to solve a problem or the application of a new method to solve a problem. Innovation can cover design, analysis, and conduct of clinical trials. Chi then discussed an innovative design—the prospectively designed two-stage or multi-stage design—to overcome limitations of the traditional, single-stage, fixed sample size design. Three references were given: Bauer and Kohne (*Biometrics*, 50:1029-1041, 1994), Proschan and Hunsberger (*Biometrics*, 51:315-324, 1995), and Fisher (*Statistics in Medicine*, 17:1551-1562, 1998).

Problems with analyses that required innovative strategies were discussed. He referred to sample size re-estimation in group sequential trials referencing, among others, Shih (in Peace K.E. *Biopharmaceutical Sequential Statistical Applications*, Marcel Dekker; 285-301, 1992) and Shen and Fisher (*Biometrics*, 55:in press, 1999). Increasing the sample size, changing primary endpoints, and dropping an arm or two were given as some reasons for modification of a group sequential trial design based on data accumulated at an interim look. The analysis of multiple or recurrent events also needs innovation. Chi cited the methodological development by Andersen and Gill (*Annals of Statistics*, 10: 1100-1120, 1992) and the more recent advances made by Lin, Wei, and Ying (*Biometrika*, 85:605-618, 1998) and Yang, Lin, Ying, and Wei (unpublished manuscript, 1998) that should result in more efficient design and analysis.

Problems exist in the presence of multiple endpoints. There is a disconnect between the proposed primary endpoint(s) and secondary endpoints and the actual clinical decision rule used to assess the strength of evidence of a treatment effect. Furthermore, there are instances where the clinical decision rules used lack appropriate statistical support structures (Chi, *Drug Information Journal*, 32:1347S-1362S, 1998).

Chi concluded that innovative methodology should have a fall-back position, if possible. Innovative methods should be evaluated on a case-by-case basis. When no existing method is available, the method should be carefully evaluated through discussion.

Discussion

Susan Ellenberg, Director in the Division of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research (CBER), FDA, discussed each of the preceding presentations. She noted that the standard method may not be quite on target for some applications and that new methods may improve upon the standard approval approach (e.g., Cox proportional hazard method). Regarding the use of new methods in regulatory submissions, the use of the optimal approach is always encouraged. It is natural for FDA reviewers to be cautious about a possibly unrecognized false positive bias with a new approach. Moreover, a reviewer’s time to learn, critique, and review new methods is limited. Current problematic areas include missing values and multiple outcomes.

For Bear’s presentation, Ellenberg said that the last observation carried forward (LOCF) is almost always inappropriate. The “worst-case” scenario, as a type of sensitivity analysis, is useful but incomplete. Multiple imputation methods are being increasingly applied. She emphasized that its underlying assumptions must be fully appreciated and clearly specified. For Ling’s presentation, Ellenberg said that, for the proportional assumption approach, the justification for the procedure and its assumptions should be clearly laid out. Sensitivity analyses would be helpful here, along possibly with a profile of characteristics of patients with missing data in each treatment group.

In her conclusion, Ellenberg agreed that standard methods are unsatisfactory for many problems. Nevertheless, FDA reviewers need to assure themselves that new methods are not flawed in important ways. Discussions of and publications on demonstrating the application of the new method will increase understanding of its advantages and potential value in the regulatory setting.

5. Issues Related to Implementation of MedDRA

One of the outcomes of the ICH initiative is the agreement to standardize the coding of medical information. The purpose of this session was to increase awareness of the chosen dictionary, MedDRA. The session covered its current timetable for implementation, its impact on the industry, its intended use by regulatory authorities, and its maintenance.

Katherine Voss, Manager of Clinical Data at Scios, chaired this session. Charles F. Thayer, Senior Director of Global Drug Surveillance and Pharmacoepidemiology at Hoechst Marion Roussel, spoke on “Implementation of MedDRA in a Pharmaceutical Company.” Miranda Rees, Director of Statistics at Roche Global Development, spoke on “MedDRA—Early Experiences with Implementation.” Andrea Neal, Senior Program Management Officer in Pharmacovigilance and Epidemiology at CDER, FDA, spoke on “MedDRA Implementation.”

These three complementary presentations, and the amount of subsequent questioning and comments from the audience, showed that despite the many years of discussion there is still a lot of work to be done and the specifics remain a mystery to most. Companies will need to change processes to implement MedDRA. The challenges are not just technical;

in fact, the impact is far greater than merely a new technical tool. As the presentations highlighted, many process issues need to be discussed and resolved at the company, and even project, level. Each company needs to take MedDRA very seriously and should start implementation planning without delay.

6. Statistical Strategies for Improving Process Optimization and Technology Transfer

The objective of this session was to obtain an overview of statistical methods and associated logistical strategies that can be used to improve the process of product development, scale-up, and transfer to manufacturing. Working closely with scientists and engineers, statisticians have contributed to significantly reduced cycle-time and improved reliability in materials and computer-chip industries. A question posed was: Can the pharmaceutical industry do the same? Better cycle times can yield shorter times to market and improved reliability can reduce regulatory risk. The session covered what it takes to achieve this and the roles that the statistician can play.

John Peterson, Associate Director of Statistical Sciences at SmithKline Beecham Pharmaceuticals, chaired the session. In addition to the presentations summarized, Tom Wrzosek, Senior Statistician of Statistical Sciences at SmithKline Beecham Pharmaceuticals, delivered the presentation "DOE [Design of Experiments] Success in Technical Transfer—Leverage to Where?"

Application of Integrated Quality Engineering Software to Pharmaceutical Process Development

Barry Evans, a statistician at Glaxo Wellcome Inc., discussed Starfire, an integrated quality engineering software system, tested at Glaxo Wellcome through a pilot evaluation conducted over a six-month period by a cross-functional team representing Pharmaceutical Development, Technical Operations, and Statistical Services. Starfire provides a structured, disciplined methodology to optimize the development and control of manufacturing processes. It provides a framework for performing statistical and quality engineering techniques including cause and effect diagrams, gauge repeatability and reproducibility studies, quality function deployment, failure mode and effects analysis, design of experiments, process capability analysis, and statistical process control. Although used extensively in the semiconductor industry, Starfire is just being introduced to the pharmaceutical industry. During the pilot evaluation at Glaxo Wellcome, the Starfire methodology was applied to the development of a manufacturing process for new metered dose inhalation aerosols.

Evans briefly described each of the statistical and quality engineering tools used by the software providing examples from the pilot evaluation. Several insights into the aerosol manufacturing process were obtained during the pilot evaluation. These included identification of measurement devices with marginal capability, identification of a critical process parameter previously believed to have insignificant influence, and development of efficient in-process controls for the filling

operation. Although the duration of the pilot evaluation was too short to realize the full potential of the Starfire methodology, several advantages of using the software were identified including the use of team-based activities to identify process elements, the creation of a process knowledge database which improves the accessibility of development information, identification of critical process elements, and the use of a disciplined approach to process development and control.

Through the pilot evaluation, Glaxo Wellcome concluded that Starfire has the potential to enhance the business process for secondary technology transfer and pharmaceutical process development, and thus plans to increase the use of this methodology in 1999 and beyond.

Faster, Cheaper, Better: Using Statistically Designed Experiments to Set and Check Process Windows

Bert Gunter, Statistical Scientist in Biometrics Research at Merck Research Laboratories, provided a brief overview of why and how statistically designed experiments can greatly improve how process tolerances are set and verified for pharmaceutical production. At each step in drug, chemical, or fermentation production processes, there are Critical Process Parameters (cpp's) that must be defined and specified as part of New Drug Applications. Examples of these parameters are pH, temperatures, concentrations of reagents, and rates of addition with specifications typically of the form target +/- tolerance, for instance, pH = 6.2 +/- 0.2. Submissions must demonstrate that maintaining cpp's within such specified limits keeps critical product quality characteristics within their required limits.

A key requirement for such demonstrations is understanding process "sensitivity," that is, how output quality characteristics change due to (small) changes in cpp's. Gunter discussed how one could systematically investigate this using multivariate screening experiments. He also briefly discussed simultaneous optimization for both quality and efficiency using robust design methods.

The essence of his presentation was that the response surface of (average) process performance as a function of controllable process parameters completely characterizes system behavior. The goal of any experimental design should therefore be to choose settings of experimental variables at which to run experiments that provide as much information on the response surface shape (for yield, purity, quality characteristics, etc.) as possible. Two-level factorial designs are effective tools to do this. They keep design sizes small, analyses simple and user-friendly, and work well. Moreover, there is readily available, scientist-friendly software for design and analysis that expresses results statistically or graphically, so these approaches are accessible even to those with minimal statistical training.

Gunter concluded that statistically designed experiments are efficient, systematic ways to set and evaluate process windows, thus improving efficiency and reducing the number of surprises in manufacturing. They also provide sound statistical and scientific justification for process specifications to the FDA. Because the methods are powerful, flexible, and simple, he concluded that they should be routinely and widely used in the pharmaceutical industry.

7. ICH Update (E5, E9, E10, and CTD)

Frank Rockhold, Vice President of Biostatistics and Data Management at SmithKline Beecham Pharmaceuticals, chaired this plenary session. He also gave an update on E10 for the choice of a control group in clinical trials. He said that they are currently at (or near) Step Two (Public Comment period) of the ICH Process.

Rockhold discussed the purpose of E10, which discusses strengths and weaknesses of most types of controls in trials. The focus of E10 is on efficacy trials. The limited use of placebos in certain areas of the world and for some diseases due to ethical issues was highlighted. Also highlighted was the sensitivity to drug effects, particularly assay sensitivity of studies intended to show non-inferiority or equivalence. Assay sensitivity is specific to a particular clinical trial, whereas sensitivity to drug effects is determined from historical experience that refers to a general set of conditions for clinical trials to detect an effect. Different types of control were mentioned—placebo, no treatment, dose response, active, external, and multiple. For each type, consideration must be given to, among other things, its ability to minimize bias and to adhere to ethical and practical issues, and its usefulness. What's next? ICH E10 will be available for public comment. It is important to engage clinical and regulatory affairs colleagues in discussions.

Stephen Ruberg, Vice President of Biostatistics and Data Management at Hoechst Marion Roussel, covered the main aspects of the ICH Common Technical Document (CTD). The outline of his talk included administrative/product label, executive summary, overall written clinical summary, clinical study documents, and raw data. The overall written clinical summary covers clinical pharmacology, clinical efficacy, and clinical safety. The clinical study documents, which provide a way to compile study reports, cover bioavailability and bioequivalence, human pharmacology, therapeutic exploratory, therapeutic confirmatory, and other related information (using cross-referencing to avoid duplicate information.)

Robert O'Neill, Director of the Office of Biostatistics at CDER, FDA, also presented. In his presentation he mentioned that "Guidance on Statistical Principles for Clinical Trials" can be found on the World Wide Web at www.fda.gov/cder/guidance.

8. Measuring and Improving Performance within Drug Development

Hugh Donovan, Vice President of Global Data Management at Hoechst Marion Roussel, chaired this plenary session which looked at various aspects of measuring performance within the drug development process from discovery through approval. Topics covered key performance indicators, measures of information collection and evaluation, and the use of such indicators and measures to improve performance.

Assessment Standards

Roger Williams, Deputy Director in CDER at FDA, and Director in the Office of Pharmaceutical Science, spoke about the impact of new guidances on drug development in industry and regulatory review at FDA. Via a series of coordinating committees, working sometimes in ICH, a series of guidances

have been finalized in CDER that provide recommendations to sponsors on a wide variety of topics pertinent to new or abbreviated new drug applications. Topics covered in the guidances include safety and efficacy, clinical pharmacology, pharmacology toxicology, biopharmaceutics (bioavailability and bioequivalence), chemistry, manufacturing and controls, microbiology, adverse event reporting, and many other topics as well. ICH has taken on, as a new document for its phase 2 efforts, the goal of developing a common technical document (CTD), or core dossier, that will create a structure for the information developed by a sponsor for submission, for instance, in a NDA.

Although the development of the CTD is still in progress, its structure is emerging as having three parts. These parts cover efficacy (clinical safety and efficacy), safety (nonclinical pharmacology and toxicology), and quality (chemistry, manufacturing, and controls). Supporting each topic are the numerous ICH and domestic guidances that are now or will soon be available. Some guidances include, as a concept, review standards—that is, an understanding of how the FDA will consider submitted data to reach a regulatory conclusion. The concept is not new and has been applied in the area of bioequivalence, for example, for many years.

In the ICH Q6A document, a specification is now defined as a series of tests, test methods, and acceptance criteria, to assure product quality at the time of batch release into the marketplace. Analogously, bioequivalence may be viewed as a 'one-time' specification where the test (bioequivalence) is addressed by certain test methods (pharmacokinetic, pharmacodynamic, comparative clinical, in vitro), and the acceptance criteria may be set a priori. New criteria to allow comparison of bioequivalence metrics were discussed briefly in the context of review standards. The concept of specification is broadly applicable, even to areas outside of product quality, for example clinical pharmacology, and relates directly to three primary questions in any scientific study: 1) what is the question; 2) what can be relied on to answer the question; and 3) how confident do we need to be in the answer. The approach of review standards allows predictability of review outcome and also can direct scarce review resources to review activities where the need for careful scientific evaluation is most important.

Measuring the Study Design Factors Which Increase Data Volume

Harold Glass, President of DataEdge, outlined his presentation with the challenges stemming from protocol complexity and patient volume. The challenge comes from more sites; site volume is exploding. More protocol complexity stems from inclusion and exclusion criteria and increased procedures. The goal is to take work out of the protocol by eliminating unnecessary treatment data and unnecessary volume.

A specific case study on arthritis showed that complexity varies by type of drug within an indication. The mean number of procedures was different by drug type. Protocols from the United States and Europe showed similar complexity. Protocols from larger companies were more complex than those from smaller companies. Lab procedures contributed heavily to the overall complexity. There was a difference in complexity between osteoarthritis and rheumatoid arthritis. The average Phase III protocol had 24 enrollment criteria,

with the number growing. There was a lot of unnecessary screening for which data needed to be processed.

Glass discussed a Phase II European study on asthma that was conducted three years ago. The number of asthmatics in an electronic database was used to determine how many would pass the enrollment process. A total of 96,000 asthmatics qualified. A distribution of the flow rate differences by subgroup (e.g., age, smoker) suggested that 93% of the asthmatics would not qualify for the Phase II protocol. The enrolled group had better flow rates than the group that was screened out. An implication from the Phase II European study is that relevant data can be captured, and data volume reduced, by screening for specific target populations.

Measuring the Pace of Change in New Drug Development

Kenneth Kaitin, Director in the Tufts Center for the Study of Drug Development (CSDD) at Tufts University, outlined the industry performance goals for the new millennium: increase the number of products in pipeline, reduce attrition rate, cut discovery and development time, contain research and development cost, and market blockbuster drugs. He said that development times and costs are increasing because of new market and regulatory demands, increased scientific knowledge, and inefficiencies in the development process. More studies plus more patients plus more procedures translate into more time and more money required to bring a new product to market.

Kaitin discussed the initiatives prompted by FDAMA to streamline clinical research. These include reducing IND requirements, codifying approval based on one pivotal trial, reviewing of clinical holds within 30 days, utilizing scientific advisory panels for dispute resolution, and establishing new FDA/sponsor meeting procedures. Ways were offered to improve efficiency.

There are two types of benchmarking: external and internal. For agency performance, for instance, external benchmarking is manifested in the rate of new drug introductions, speed of the approval process, and number of safety withdrawals relative to other pharmaceutical markets. Internal benchmarking includes trends in review times, user-fee drug approvals, and process improvements. CSDD offers benchmarking tools: annual confidential reports to firms, published trends analysis, published current status reports, and specific information requests.

In his conclusion, Kaitin noted that we are in era of unprecedented challenge and opportunity for pharmaceutical innovation. High drug development times and costs have led to a collaborative effort to improve efficiency in the development process, lower expenses, and focus on important new therapies. Making appropriate use of high-quality benchmarking metrics can help to improve both industry and FDA performance.

9. The Validation Step—What Does It Mean to Statisticians and Statistical Programmers?

In this session speakers from industry discussed concepts, principles, and techniques of program development and validation which are relevant to statistical programming in the

clinical trials setting. Validation procedures that have been developed and applied to statistical programs, written by statisticians and statistical programmers, were described, along with procedures for overseeing the interface between statisticians and statistical programmers. The FDA perspective on issues concerning validation in this setting was also presented.

Steve Wilson, Team Leader in the Division of Biometrics II at CDER, FDA, chaired the session. Ji Zhang, Director of Biostatistics at Merck Research Laboratories, presented "Considerations and Experiences in the Developments of a SOP for Statistical Software Validation." Mike Boyd, Director of Biostatistics, and Lee Walke, Manager of Clinical Programming, from Pharmaceutical Research Associates, Inc., were joint authors of the presentation "Taking Steps to Ensure the Accuracy of Statistical Reporting." Judith D. Goldberg, Vice President of Biostatistics and Data Management at Bristol-Myers Squibb Company, and Peter A. Lachenbruch, Chief of the Biostatistics Branch at CBER, FDA, served as discussants.

10. Data Management Metrics

David Mailhot, Associate Director of Biometrics at Pfizer Central Research, chaired the session on data management metrics. Data management is subject to constant performance measurement through the use of metrics because the units of work, that is case report forms and queries, lend themselves easily to measurement. This session provided an opportunity to learn how different companies measure data management-related activities and, more importantly, how they use them to evaluate and improve performance.

Metrics: Not for the Meek

Armelle Pitre, Senior Associate Director of Biometrics at Pfizer Central Research, defined metrics as "A proven quantitative set of measurements for costs, productivity, efficiency, effectiveness, timeliness, and quality."

Metrics can be used and viewed as a triumvirate with strategic, procedural, and operational compartments. An integrated approach to using metrics featured the interdependence of procedural, operational, and strategic elements, bonded by a continuum of feedback. Pitre identified and described measurable factors of volume, timeliness, quality, and cost and resources. A discussion followed on the presentation and evaluation of metrics through the use of tables and reports, ratios, summary and detail, and links to goals. She described in detail an evolving metric life cycle and examples of the usefulness of metrics. Several types of ratios were illustrated, for example, number of outstanding queries to total number of queries and number of queries to total number of subjects.

Pitre provided metrics maxims. Metrics should be based on key process deliverables and goals. They must be quantifiable and should be timely and practical. The evaluator must be prepared to refine metrics continually as the process changes. Metrics should not be used out of context as it is likely to alter behavior; metrics should not be necessarily used for performance evaluation. Metrics should not be used to punish or blame individuals. Finally, metrics states what, when, how, and who—but not why.

Clinical Data Management (CDM) Metrics: A Necessary Evil Made Simple

Brenda Hoepfer, Associate Director of Data Management at Kendle International, began with quotes on the meaning of the word "metrics." She defined metrics as "the collection of quantifiable data for the purpose of measuring a specific activity or group of activities." Metrics are important to collect because they measure success, failure, and impact, as well as process improvement. Metrics are important for resource planning, evaluating and establishing cost, and ongoing and historical performance. Consistent, ongoing, simple, and target oriented—these are the four principles of CDM metric collection methodology. In discussing on how metrics can be helpful, Hoepfer described CDM task codes, electronic timesheets, and tracking, with specific examples. Because not all projects should be treated equally, an issue for metrics is its potential to be misused and misinterpreted. In closing, Hoepfer emphasized that the collection of data for the purpose of measuring an activity or group of activities does not need to be painful or time consuming.

Modernizing Metrics

Hugh Donovan spoke on the changing environment. He described why and how we currently measure our performance, how we should rate ourselves, the disconnect between the current situation and ideal situation, and the use of metrics to address the gap. Today the organizational structure is typically matrix-based with an emphasis on project/study teams. He raised the question whether current metrics reflect this team dimension.

Donovan mentioned that the results of a recent survey by the Society for Clinical Data Management showed that metrics are used to track progress against timelines, to gain knowledge for improved planning for future studies, to measure the impact of new technologies or systems, to assess objectively and consistently staff performance, and to inform other functions in an organization about CDM and its activities. He presented the top metrics from the survey. These included number of queries issued to investigators, number of case report form (CRF) pages entered, error rate, time from query issued to query resolved, time of last CRF page in-house to database lock, and time from CRF receipt to data logged.

Donovan made several observations about metrics. A summary report card was proposed as a more meaningful indicator of performance than current metrics. The report card includes the percentage of databases meeting quality standards, the percentage of activities within time (by activity), and the cost of certain activities (e.g., CRF pages processed, errors detected).

11. Data Mining in the Pharmaceutical Industry

Frank Shen, Director of Nonclinical Biostatistics at Bristol-Myers Squibb Company, chaired this session. While glittering words like "Data Mining" have attracted much attention in the industry, biostatisticians may not fully understand what the scope of data mining is and where the mining opportunities are. Can conventional statistics based upon hypothesis testing and sampling theory take the chal-

lenge from the paradox raised by exploring established massive data warehouses? Can statisticians work seamlessly with computer scientists to expand the definition of "Exploratory Data Analysis" and accommodate data mining as a statistical practice? Who can be classified as data miners? In this session three scientists and statisticians from drug discovery and development discussed the opportunities for data mining in the pharmaceutical industry and how statisticians can get involved.

Stanley Young, Principal Consultant at Glaxo Wellcome Inc., presented "Overview on Data Mining." Dan Davison, Principal Scientist of Bioinformatics at the Pharmaceutical Research Institute at Bristol-Myers-Squibb, presented "Data Mining Approaches to Understanding Genomic Sequence Data." David J. DeBrot, Clinical Research Physician in Neuroscience Research at Eli Lilly and Company, presented "Mining Clinical Trial Data." He discussed whether "data mining" (as he defined it) is truly possible in 'clinical trial data', and also discussed the differences between statisticians who are focused on the support of registration dossiers and those who are involved in purely exploratory analyses of data. The session was well attended with very active floor discussions.

12. Defining Substantial Evidence to Assess Effectiveness for Drug Products

This plenary session had two co-chairs: Cecile Balagtas, Senior Associate Director of Biometrics at Pfizer Central Research, and Susan Ellenberg. The quantity and quality of evidence required to demonstrate effectiveness is a major determinant of drug development time and cost. For example, the FDA has generally required at least two independent and well-controlled studies to establish effectiveness. In some cases, it has also relied on a single adequate and well-controlled multicenter study demonstrating statistically very powerful findings. The objective of this session was to promote the discussion of what constitutes "statistically very powerful findings" and the methods one might use to demonstrate the strength of evidence and the robustness of results.

Defining Substantial Evidence—A Proposal

Collaborating with Bill Huster from Eli Lilly and Company, Ronald Knickerbocker, Biostatistics Evista Team Leader at Eli Lilly and Company, began his presentation by giving background information about the FDA generally requiring two adequate and well-controlled studies for approval of a new drug. He described a four-point proposal by Nevius (*ASA Biopharmaceutical Proceedings*, 1988) on assessing the primary evidence for approval of a new drug from a single multicenter trial: 1) overall analysis shows significant results, 2) consistency across centers in direction of effect, 3) consistency across centers in producing nominally significant results in centers with sufficient power, and 4) evidence of efficacy after adjustment for multiple comparisons (with a conservative Bonferroni adjustment). He also described the work of Huster and Louv (*Journal of Biopharmaceutical Statistics* 2:219-238, 1992) who addressed how to quantify whether the amount of evidence in a single multicenter trial is equivalent to that from two separate trials.

In their paper, Huster and Louv proposed a post-hoc subdivision of a multicenter trial, provided that the inherent multiple testing problem is accommodated, and a minimax statistic to test the hypothesis that the effect of drug has been reproduced in a single multicenter trial.

Knickerbocker proposed seven criteria for assessment of evidence: 1) strength of association (p -value vs. likelihood ratio); 2) dose-response—effect as a function of dose; 3) temporal relationship—effect as function of time; 4) specificity—effect after cessation of treatment; 5) consistency—effects in other patient population and for other endpoints; 6) replication—effects in other studies; 7) biological plausibility—mechanism of action. He noted that the focus has been on replication (criterion #6) and that all seven criteria need to be evaluated to assess substantial evidence. He used two case studies to illustrate how to document and quantify all seven criteria.

The Usual FDA Paradigm and Strength of Evidence

Lloyd Fisher, Professor of Biostatistics at the University of Washington, began with a background on the usual FDA paradigm and gave its pluses and minuses. The general standard of two positive randomized controlled studies has the benefit of being easy to understand and related to the strength of the evidence. The general standard, however, reflects only part of the evidence.

The presentation then focused on clearly equivalent single studies. One important possible scenario where an equivalent single-study may be sufficient is for serious, irreversible endpoints such as survival when it is neither ethical nor practical to perform a second trial. It is more challenging to rely solely on the results of a single study with an active control because we do not know what would have happened if there had been a placebo. Regarding the strength of the evidence, the p -value is a useful surrogate but is far from perfect. Every school of thought, including the Bayesian School and the Likelihood School, has limitations about p -values.

Fisher posed a series of provocative questions to stimulate the presentation. If we rank all patterns of possible outcomes in trials, the multiple comparisons problem becomes an issue, questioning the plausibility of the interpretation. He said that one hallmark of a good scientist is to learn from accumulating data and to react appropriately—not perseverating on a particular idea. Much work needs to be done. This includes reasonable modeling of development programs to get broader paradigms and methods that are more responsive to accumulating data. A reference for Prof. Fisher's talk is his article on "Self-Designing Clinical Trials" in *Statistics in Medicine* (17:1551-1562, 1998).

Discussion

Robert O'Neill mentioned that using two well-controlled randomized studies for drug approval was introduced in 1979. He showed a figure on the expected width of a 95% confidence interval for studies powered at 90% for an assumed treatment effect (effect size). He said that one-sided p -values are not the way to go. He recommended the employment of two-sided confidence intervals, with hypothesis testing being done later. Observed p -values should be smaller than you think for "statistical significance." In making his point, O'Neill highlighted the findings in the paper

by Goodman in *Statistics in Medicine* (11:875-879, 1992).

Robert Temple emphasized that in most cases the current standard of independent substantiation of the effectiveness of a drug is not onerous. To evaluate a drug's dose-response, effects in various stages of disease, duration of effect, and effect on different therapeutic backgrounds, and to obtain reasonable safety data, generally requires more than a single study. Difficulties arise when the effectiveness study is very large, when one study shows an important clinical benefit, such that it is ethically difficult or impossible to obtain more data, and when there are in fact multiple studies but only one shows effectiveness. Temple also noted that the usual urging to consider the "totality" of the evidence is a double-edged sword; sometimes reliance on the "two studies to win" is actually a lower standard than considering all of the studies. The severity of disease should not affect the fundamental basis of approval; giving ineffective drugs to patients with serious illness is no boon, and it is not more difficult to show effectiveness in serious illness.

13. An Overview of Pharmacogenomics

Craig Trost, Director of Statistical Research Group at Pfizer Central Research, and Peter A. Lachenbruch co-chaired this session. Trost began the session by introducing the audience to the topic, including providing definitions of terms (e.g., genome, genomics, structural genomics, functional genomics). Even though the work is not completed, the Human Genome Project is beginning to change the pharmaceutical industry. Biostatistics needs to invest heavily in the new methods that will be required to handle these new data.

Trost noted that the impact on the field of biostatistics could be substantial. Biostatistics will be involved from the discovery of new drugs all the way through marketing. Currently the field of bioinformatics is dominated by computing. Unfortunately, most in this field know little about statistics. Safety evaluations may involve genotyping of metabolic pathways while efficacy may be targeted to subpopulations based on genotype. In the marketplace genetic diagnostic tests may be used to determine dosages or to predict adverse events. The nature of clinical trials could change significantly. We need to begin now working on methods that will meet the needs of both the industry and the regulatory agencies. During this session, an overview of pharmacogenomics from a biostatistical viewpoint and its potential impact on drug development were presented.

Genes, Chips, and Genomes

Robert Lipshutz, Vice President of Corporate Development at Affymetrix, Inc., discussed photolithographic synthesis, synthesis of ordered oligonucleotide arrays, wafer and chip format, photolithography and synthesis density, Genechip[®] Manufacturing Technology, array designs, and yeast genes. Lipshutz, a mathematician, continued his technical discussion of expression monitoring by highlighting the requirements for 1) sequence information, 2) 100 ng Poly A mRNA, 3) labeled nucleic acid, 4) chips, and 5) hardware/software. He also described the following areas: hybridization signal vs. target concentration, expression monitoring mRNA abundance, preparation of labeled target,

array controls, tolerated uncertainties, and oligo probe selection.

Lipshutz discussed a specific gene expression experiment that demonstrated fidelity of absolute intensity (yeast DNA), mRNA distribution (yeast), reproducibility, yeast gene expression (rich medium vs. minimal medium), and differential expression (rich medium vs. minimal medium), among other areas. He described chip and gel-based solutions for genetic mapping. Accuracy and reproducibility were covered. The experiment and results of a genotyping with a Poly300 chip were presented. Genotype common variances and current methods of gel-based solutions were articulated.

Panel Discussion

Philip Noguchi, Director in the Division of Cellular and Gene Therapies at the FDA, raised the question of whether the gene procedure works. Noguchi highlighted a recent article in *Science* (282:1145-1147, 1998) on deriving embryonic stem cell lines. Social implications were mentioned.

Daniel Holder, Senior Biometrician at Merck Research Laboratories, provided an introduction to hunting for human disease genes. The process involves establishing a genetic component, collecting families, performing a genome-wide scan (i.e., finding genetic markers associated with affected individuals), and doing fine mapping (i.e., finding genes between the markers). He commented on the potential problems including multiplicity, the limited use of the case-control design, and how study of transmission of genetic material down through a pedigree is more effective than looking across populations.

Holder noted that, since complex pedigrees lead to complex correlations, statistical methods relying on the assumption of independent and identically distributed random variables are of limited use. Likelihood and conditioning are the most common methods of analysis. The immediate goal of most of these studies is to show linkage, that is, that the recombination rate between a marker and a putative disease gene is small. He discussed how stratification and admixture can lead to association even in the absence of linkage. He noted that fine mapping of human disease genes is difficult and there are no routine statistical methods. The success of hunts for genes for complex diseases is still in doubt.

Holder discussed the statistical opportunities in genetic research, and the many open statistical questions. Fruitful collaboration requires substantial commitment to statistical genetics and close collaboration with geneticists. Presently, most of the expertise is in academia.

14. Outcomes Research Issues In Alzheimer's Disease

Joseph Cappelleri, Associate Director of Biometrics at Pfizer Central Research, and Lisa Kammerman, Team Leader in the Division of Biometrics II at CDER, FDA, co-chaired this session, which covered three main topics. First, health-related quality of life, caregiver time and burden, health status, and service utilization were examined according to the severity of Alzheimer's Disease (AD). Second, the health utilities of AD patients (and their caregivers) were assessed in different disease stages and care settings. Third, labeling and advertising issues related to outcomes research in AD were discussed.

A discussion of these topics was provided by Lisa Kammerman.

Health Service Utilization and Caregiver Burden in Different Settings of Care for Alzheimer's Disease

Ming-Ann Hsu, Senior Associate Director of Outcomes Research at Pfizer Central Research, presented the results of a study that addressed health service utilization and caregiver burden by AD severity in different care settings (*Health Affairs* 17:206-216, 1998). This cross-sectional study involved 13 sites in the United States: 4 academic medical centers, 4 managed care organizations, 2 assisted living facilities, and 3 nursing homes. A convenience sample with consecutive enrollment of 679 AD patient/family caregiver pairs was enrolled from July to December 1996. Patients' AD stage was determined by clinicians using the Clinical Dementia Rating Scale.

Hsu said that a one-month delay in institutionalization would yield savings of \$1,862 in formal services, which included hospital days, emergency room visits, and number of physician visits. This translates to \$1.2 billion annually. But the study asserts that, although delaying entry into a nursing home could save dollars, those savings might be achieved at great expense to family members.

The study gave insight on how the managed-care industry is handling AD. Although total costs on AD—both formal and informal—appear to be the same in both managed care plans and traditional academic health centers, the managed care plans appear to place a much higher burden of care on family members. For example, informal care cost, which are unpaid and generally provided by a family member, made up more than 70% of the total costs for managed care patients, compared with 52% for patients of academic health centers. This difference translates into 43 hours of additional care per month for managed care patients.

Hsu mentioned that the 1996 annual costs associated with AD were estimated at \$14.9 billion for mildly impaired patients and \$36.4 billion for moderate/severely impaired patients, for a total of \$51.3 billion across all severity levels. She also noted that caregiver burden and stress increased with disease severity, and with AD patients being in a community setting (academic medical center or managed care plan) rather than in a residential setting (assisted living facility or nursing home).

Health Utilities in Alzheimer's Disease: A Cross-sectional Study of Patients and Caregivers

Peter Neumann, Assistant Professor of Policy and Decision Sciences in the Department of Health Policy and Management at the Harvard School of Public Health, presented his article "Health Utilities in Alzheimer's Disease—A Cross-Sectional Study of Patients and Caregivers" in *Medical Care* (37:27-32, 1999), which is based on the study described by Hsu. His presentation had two main objectives: 1) to test the feasibility of measuring health utilities in AD with a generic preference-weighted instrument using proxy respondents and 2) to assess the utility scores of AD patients (and their caregivers) in different disease stages and care setting.

Neumann said that The Health Utilities Index Mark II (HUI:2) questionnaire was administered to caregivers of patients who responded both as proxies for the patients and for themselves. Responses to the questionnaire were converted into a global utility score, between 0 and 1, using the

HUI:2 multi-attribute utility function. Global utility scores varied considerably across patients' AD stage; for the six stages assessed (questionable, mild, moderate, severe, profound, and terminal), mean utility scores were 0.73, 0.69, 0.53, 0.38, 0.27, and 0.14, respectively. In multiple regression analyses, AD stage was a negative and significant predictor of utility scores for patients; setting did not exert an independent effect. Utility scores for the caregivers were insensitive to patients' AD stage and setting.

In concluding, Neumann mentioned that patients' AD stage had a substantial influence on health utilities, as measured by the HUI:2. He noted that more research is needed to assess the validity of using proxy respondents.

Outcomes Research in Alzheimer's

Toni Stifano, Associate Director for Policy at CBER, FDA, discussed drug labeling and advertising. She highlighted the challenges for the FDA Health-related Quality of Life policy development.

Stifano said that we should do what we do for all other clinical outcomes being considered for the labeling and advertising of products. Adherence to the existing legal standards for labeling means that substantial evidence must be demonstrated. Substantial evidence comes from an adequate and well-controlled study, along with its accompanying high scientific standards. In some cases, however, reproducibility may not require duplicate studies.

In the design of studies, the minimal meaningful differences—or the smallest difference in a score that could be perceived as a benefit or change the way a patient is managed—should be prespecified. Controversy remains whether minimal meaningful difference should be correlated with an objective observed clinical endpoint or a subjective patient-perceived change. In the study design, the instrument should capture all the relevant domains in the population being studied and any negative impact of treatment. She outlined the attributes of an instrument: validity, that the instrument measures what it purports to measure; reliability, that the instrument yields reproducible scores over time; and sensitivity, that the instrument has the ability to detect clinically meaningful changes.

Stifano said that the FDA expects that the instrument used be validated and have complete documentation. The instrument should be capable of measuring the important positive and negative subjective effects of the disease and the treatment. At a minimum, the instrument should measure the following domains: physical function, psychological/emotional function, and social. Stifano highlighted what to consider in reporting the results. Results from all quality-of-life domains should be reported. Patient global scores on quality of life are best left for use only as a point of reference and generally cannot support a labeling claim.

Ms. Stifano concluded that quality-of-life endpoint assessments can provide valuable information and may have potential to be a better endpoint than existing efficacy measures for certain conditions—for example, dementia and rheumatoid disorders. The criteria for a claim on quality of life continue to develop, but are not yet defined. The use of quality-of-life endpoints in drug development and promotion is expanding. It is incumbent upon regulators to work closely with the experts to encourage the development of measurements tools

for use in drug development. It is important that sponsors work closely with the FDA to ensure that information on quality of life described on labels, in advertisements, and for dissemination be balanced, truthful, and not false or misleading.

Discussion

Kammerman discussed the three presentations, grouping the Hsu and Neumann presentations together since they were based on the same study. In her comments, Kammerman mentioned the lack of a probability sample in the estimates of costs and analysis of utilities. The conclusion that "setting does not exert an independent effect" was critiqued. She showed, with a contingency table on setting and AD stage, that setting and AD stage are correlated and recommended that the multivariate regression analyses be revisited.

Kammerman then summarized the Stifano presentation. Of particular note were analysis issues on missing data, meaningful treatment effect, and multiple endpoints and comparisons.

She raised two issues for discussion. One was the role of caregiver burden in advertising claims. The other was the role of studies of costs, patient burden, and caregiver burden in the drug development program.

15. New Approaches to Drug Discovery

This session was co-chaired by Michael Liebman, Director of Bioinformatics at Wyeth-Ayerst Research, and Edward Nevius, Director in the Division of Biometrics II at CDER, FDA. Michael Liebman spoke on "The Intersection of Bioinformatics and Drug Discovery." Isidore Rigoutsos, Manager of Bioinformatics and Pattern Discovery Group at IBM, spoke on "Motif and Association Discovery in Biology: Instances and Solutions." Greg Tucker-Kellog, Staff Scientist at Genetics Institute, spoke on "Gene Expression Analysis."

The session provided an overview of the drug discovery process as it is evolving to include bioinformatics, pharmacogenomics, and functional genomics. To date, current methods have been augmented by the inclusion of high throughput screening, combinatorial chemistry, and array technology, all of which combine to significantly expand the amount of data which needs to be analyzed. The introduction of the bioinformatic components, which can even include clinical data, presents new challenges because of the need to deal with data of a less quantitative nature. These new technologies provide both challenges and opportunities to the data analysis process.

16. Innovative Data Management Processes and Technology

The session provided details of new approaches to data management. Innovation can be found in simple streamlining of processes and in the utilization of cutting edge technology. This session was chaired by Louise M. Murphy, Vice President of Clinical Informatics at CoCensys, Inc. Paul Bleicher, Chairman and Chief Scientific Officer at Phase Forward Incorporated, spoke on "Internet Clinical Trials: Eliminating the Data Visibility Gap and the Data Quality Gap." Brent

Cliveden, from the Clinical Trial Solutions Group at IBM Global Healthcare Industry, spoke on "Speech Recognition in Clinical Drug Development." Robert J. Halstead, Manager of Clinical Data Operations at Alza Corporation, spoke on "An Example of Data Management Process Changes due to the Implementation of New Technology."

Bleicher's comprehensive review of the use of the Internet for clinical trials can be found on Phase Forward's home page. His talk summarized the advantages of on-line, real-time clinical trial data acquisition and management on the Internet. His talk indicated that the challenges in using the Internet for clinical trials are in security, performance, and availability of Internet access. Bleicher outlined the way that these challenges could be addressed, today.

Cliveden's in-depth review of the history, current status, and future use of speech recognition showed that the technology is at a stage where it could be considered for limited use in data acquisition from clinical trials. However, there are many issues related to both technology and process that need to be resolved before it can be widely implemented. He encouraged the audience to become familiar with the concepts through use of the technology in other areas, for example in the dictation and 'reading' of E-mails.

Halstead reminded the group, through a recent example, that the biggest barrier to successful implementation of new technology is usually not the technology itself but the organizational and procedural implications. Failure to consider these aspects, and to make any necessary changes, will ensure failure of the technology. He also covered ways of implementing a new technology, such as Datafax, and what his organization did well and not so well to get Datafax up and running.

17. Modernizing Organizational Processes in Pharmaceutical Research and at the FDA

Frank Rockhold and Charles Anello co-chaired this session. Gregory Enas, Director of U.S. Regulatory Affairs at Eli Lilly and Company, and Robert O'Neill were the two speakers. They gave talks presenting their approaches to organizing statistician and data management organizations for success in the 21st century. Each speaker discussed how biometrics is organized, what role each type of person plays in the organization, what project focus each person has, what influence each person has with decision makers, and what skills set and educational background/training are required for each role. The two 25-minute presentations were followed by a 15-minute panel discussion of questions and answers where people had an opportunity to assess the gaps and affinities between the two organizations, including how the changes may influence the interaction between industry and FDA.

18. Career Achievement Award and FDA Visitation Panel Discussion

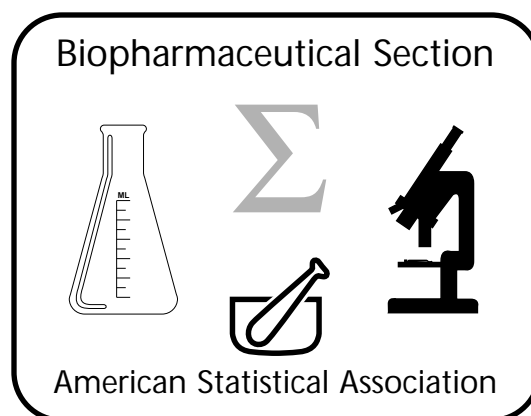
During the first luncheon, Lyman Ott, Senior Vice President at Hoechst Marion Roussel, received the Biostatistics Career Achievement Award for life-long contributions to the pharmaceutical industry and the statistics profession. This prestigious honor is annually bestowed to a biostatistician or clinical data manager who has made significant

contributions to these fields and their applications in the pharmaceutical industry.

At the second luncheon, there was a FDA Visitation Panel Discussion in which the FDA and sponsors shared learnings, successes, and directions for enhanced collaborations. Among the items discussed were the FDA's intention to visit and interact more closely with smaller and medium-sized pharmaceutical companies, while maintaining a close interaction with larger companies. Representatives from the FDA included Steve Wilson and Edward Nevius. Industry representatives included Robert Knickerbocker from Eli Lilly, Stephen Ruberg from Hoechst Marion Roussel, Keith Soper from Merck, Krishan Singh from SmithKline Beecham, and Liannng Yuh from Pfizer.

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Section News

Letter from the Chair

Kenneth J. Koury

In the recent past, the Biopharmaceutical Section has been one of the largest and most active Sections of the ASA, and 1998 was no exception. The strong programs offered by the Section at ENAR in Pittsburgh and the JSM in Dallas were perhaps the most visible of our accomplishments. These programs, along with Section-sponsored short courses and workshops, provide excellent opportunities for participation by Section members, as well as direct benefits to the large number of members who attend these meetings. We are grateful to Tom Capizzi, 1998 Program Chair, for organizing such an extensive and well-received program, highlighted by seven invited paper sessions at ENAR/JSM, four special contributed paper sessions and two short courses. And thanks to Richard Entsuah for organizing six round table discussions at the JSM.

The Section also co-sponsored the Midwest Biopharmaceutical Statistics Workshop in May, held at Ball State University in Muncie, Indiana, and the Deming Conference on Applied Statistics, held in December in Atlantic City, NJ. Another highlight of 1998 was the Third Annual FDA-Industry Workshop, co-sponsored by the Section and the FDA Statistical Association, and held in Alexandria, Virginia in September. The workshop committee, led by Bob Small, developed an excellent program; registration was outstanding with nearly 300 attendees, including more than 75 FDA statisticians. Ralph Harkins and Nancy Smith will chair the 1999 Workshop.

For the second year in a row, over 100 members attended the Section Mixer and Business Meeting at the JSM, where the winners of our Best Presentation Competition and Student Paper Competition were introduced. In order to promote higher quality presentations at the JSM, the Section awarded plaques and a total of \$1,000 to the first, second and third place winners based on presentations of contributed papers at the 1997 JSM. Thanks to our members who completed the evaluation forms during the sessions and to Sandy Heft for organizing the competition, distributing and collecting forms, and determining the winners. Sandy also ran the 1998 Competition, and he has already notified the winners who will receive the awards at our Business Meeting during the 1999 JSM. Ji Zhang chaired the Student Paper Competition Committee that was created to encourage student participation in our program at the JSM and the development/implementation of statistical methods for biopharmaceutical applications. Five winners were selected for 1998, and each was presented with a plaque and a cash award of \$1,000. The Section also contributed \$500 to support the 1999 Undergraduate Data Analysis Contest and \$500 to support the 1999 Poster Competition.

Over the past couple of years the Section created three important committees. The Fellows Committee, led by Larry Gould with Bruce Rodda and Charlie Goldsmith, identifies candidates and facilitates completion of the nominating material in order to support the election of Section members as

ASA Fellows. Congratulations to the seven members who were elected as Fellows in 1998.

The Membership Committee, led by Phil Pichotta, has done an outstanding job of attracting new members and keeping current members informed of the Section's benefits and services. At the JSM members received a letter in their registration packages reminding them of Section-sponsored activities, as well as a sticker for their badge to identify them as members of the Section. A new membership drive was implemented in the Fall; and although Phil moves off the Executive Committee, we are fortunate that he will remain as Chair of the Membership Committee—like the *Energizer Bunny*, Phil just keeps rolling along!

In order to emphasize the importance of communicating with our members, a Communications Committee, led by Denise Roe, our Publications Officer, was created to coordinate the news and announcements related to Section activities. Denise developed a schedule so that every issue of *Amstat News* will highlight and remind members of upcoming events. Sally Greenberg created and has maintained the Section Web site and Electronic Mailing List. Kalyan Ghosh and Laura Hawthorne will be Webmasters in 1999. Two editions of the *Biopharmaceutical Report*, the Section's outstanding newsletter, were published in 1998 by Anne Meibohm, who served as Chief Editor, with Associate Editor Ersen Arseven and Past Editor Curt Wiltse. The Section will also publish the *1998 Proceedings of the Biopharmaceutical Section*, which will include papers from Section-sponsored sessions at the JSM, ENAR, and the Midwest Biopharmaceutical Statistics Workshop.

As the New Year begins, the Section is in very capable hands. For 1999, Steve Snapinn is the Section Chair and Christy Chuang-Stein is our Program Chair. Steve has been an active member of the Executive Committee for several years and served as Program Chair in 1996. Christy has already finalized an excellent invited program for the coming year, and members should note that it is not too early to think about invited sessions for the year 2000. Contact Bob Small, our Program Chair-Elect, with any ideas or proposals, as the invited program for 2000 will be close to final by the time we meet at the 1999 JSM in Baltimore. Thanks also to Sally Greenberg and Chuck Davis for representing our interests on the ASA Council of Sections. Sally's term ended in December, but she now begins a three-year term as Secretary-Treasurer.

Finally, I would like to extend special thanks to two key members of our Executive Committee whose terms have just ended—Bob Davis and Jeff Meeker. Jeff served as Secretary-Treasurer over the past three years. His thorough, accurate, and prompt minutes, as well as his knowledge and experience in operating within the ASA framework, were valuable resources, and he kept us on a sound financial path. Bob has been an outstanding member of the Executive Committee for six years—first as Secretary-Treasurer and then as Chair-Elect, Chair and Past-Chair. He played a major role in shaping the current organizational structure of the Committee so that we can efficiently run all of the Section-sponsored activities described above. And Bob's influence will continue for years based on his appointments and the exceptional slate of candidates that he organized for the upcoming elections. His advice made most of our decisions easy, and his sense of humor was a bonus. Like *Dunkin' Donuts*, it was always worth the trip, just to hear Bob's jokes!

Third Annual FDA-Industry Workshop

Bob Small

The third annual FDA-industry workshop took place September 24–25 in Arlington, Virginia at the Regency Hyatt Crystal City. The Biopharmaceutical Section and the FDA Statistical Association sponsored the workshop this year. The overall meeting was a significant success with attendance exceeding 275. There were over 75 FDA statisticians in attendance with significant numbers of representatives from industry, academia and foreign countries.

The theme of this year's meeting was "Current Statistical Issues in Drugs, Biologicals, Medical Devices, and Risk Assessment." The seven sessions reflected the diversity of interests suggested by the theme and could be grouped into three categories: an FDA update, statistical methods and issues, and reviews of other areas of interest to statisticians in industry.

The workshop opened with a session in which members of the FDA updated attendees on developments affecting industry-regulatory relationships. First, Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research gave an overview of the FDA Modernization Act. Then Susan Ellenberg, Director of the Division of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research gave an update on ICH issues. Finally, Steve Wilson discussed the FDA's evolving views on Electronic Submissions.

The four sessions on statistical issues were GEE Models, Issues in the Use of Controls, Bayesian Methods in Pharmaceutical Development, and Computer Intensive Methods. These sessions followed a similar format. The first speaker, usually an academic, presented an overview of the topic which was followed by the presentation of specific issues from industry and FDA points of view. The overviews were presented by Ron Helms (GEE Models), Jay Siegel (Use of Controls), Don Berry (Bayesian Methods), and Cyrus Mehta (Computer Intensive Methods).

Two areas not previously covered in our workshops were addressed with overview sessions. In a session on Diagnostics, Greg Campbell of the FDA, J. Kennedy, a consultant, and Colin Begg of Memorial Sloan Kettering gave talks on issues that arise in the evaluation of diagnostics. A session on Risk Assessment featured Dave Gaylor of the FDA's Toxicological Research Center giving an overview of risk assessment issues. Professor C. Yoe of the College of Notre Dame gave a talk on risk assessment and management from a policy point of view, and R. Buchanan of the FDA discussed techniques for quantitative microbial risk assessment.

Attendance at the meeting exceeded expectations and the turn out of FDA statisticians helped make the meeting a particular success. There was a mixer on the night of the first day of the workshop that gave all a chance to exchange views with industry, academic and government colleagues. The speakers exemplified the diversity at the meeting as well. There were five academic, five industry and 10 government speakers. Of course, the FDA update session supplied three of the government speakers.

The Biopharmaceutical Section Executive Committee has decided to sponsor another Workshop next fall. Nancy Smith of the FDA and Ralph Harkins of Quintiles will be co-chairs.

ASA Fellows Nominations

Larry Gould

Chair, Fellows Committee

We were exceptionally successful this year in having Biopharmaceutical Section members elected Fellows of the ASA. The Section believes that this success can be continued in coming years because there are many Section members whose contributions to the profession and to society merit this honor.

One way that we can achieve this success is by each of you thinking about one or more colleagues who would merit nomination for Fellowship. You can include yourself, by the way. The process by which Fellow nominations are put together is not difficult, and people who have put successful nominations together can provide hints that may be helpful. The Fellows Committee was created by the Section to help you identify worthy candidates and to help with putting a nomination together.

This article is a first step toward achieving that goal. Included are a request from the ASA for Fellows nominations, a summary of the key points from an informational meeting held by the ASA Fellows Committee during the JSM this past August, and some hints on preparing nominations that Bob Starbuck compiled a while ago. A letter from the chair of the ASA Committee on Fellows which describes the nomination process, guidelines for justification of nomination, guidelines for letters of recommendations in support of potential fellows, a nomination form, and examples of citations for fellows are available on the ASA Web site (www.amstat.org). All of this information is also available on the new Biopharmaceutical Section Web site (www.best.com/~asabp) or from me. Finally, John Schultz, the ASA Committee on Fellows Chair, has pointed out that the committee members review a lot of nominations and appreciate nominations that are brief, complete, well organized, documented, and to the point.

Given the time required for the various steps, it would be worthwhile to get started now. The Section can co-sponsor a limited number of nominees, but most of a nomination must be in hand in order for this to happen. A nomination still can go forward without Section co-sponsorship. Some did this year, and were successful.

If you have any questions, please call me at (610) 397-2525 (E-mail goulda@merck.com) or the other members of the Fellows Committee: Bruce Rodda at (512) 685-5855 (E-mail bruce.rodde@austin.ppd.com) or Charlie Goldsmith at (905) 522-1155 ext 4903 (E-mail goldsmith@fsu.csu.mcmaster.ca).

ASA Fellows Nominations Requested

The Committee on Fellows enlists your help in the nomination of new Fellows. Members must have a nomination form submitted on their behalf to be considered. Committee members do not offer nominations themselves; but we encourage the general membership, Chapters, and Sections to make a thorough search for deserving candidates. All too often we receive nominations for outstanding members who somehow have been overlooked for years.

While the Committee relies upon members to nominate worthy candidates, it is our responsibility to ensure, to the best of our ability, that the most deserving nominees are chosen. In reaching these decisions, the Committee relies heavily upon the facts and opinions contained in supporting letters and documents. It is important that the nomination describe the nominee's most important contributions, which can be in the advancement of theory, consulting, teaching, applications, data collection, administration, and service to the Association. We judge actual contributions, not future promise. Outstanding work in related fields (economics, psychology, etc.) is judged in terms of its contribution to the field of statistics.

Please be sure that anyone you nominate has been a member of the Association for at least three continuous years prior to the deadline date and is not already a Fellow of ASA.

Please give careful attention to all instructions on the nomination form. Nominations must be received no later than March 1, 1999. Previous nominations are not carried over, but candidates may be renominated. We recommend that supporting materials for renominations be updated.

Key Points From ASA Committee on Fellows: Informational Meeting August 12, 1998

Criteria (see also guidelines on ASA Web site)

Many Roads Lead to Fellowship:

1. Recognize ASA members "who have made outstanding contributions in some aspect of statistical work" (ASA By-Laws)
2. Give "due weight to publications, the position held by the candidate in the organization in which the individual is employed, activities in the Association, membership and attainment in other societies, and other professional activities ... with no one of these criteria governing selection to the exclusion of others" (ASA By-Laws)
3. Nomination form requires
 - a. Supporting statements on small number among: consulting on statistical problems; statistical applications and data collection; administration of statistical activities, teaching and dissemination of statistical knowledge; statistical research; activities in ASA
 - b. List of publications having statistical content
 - c. Supporting letters
 - d. Proposed citation

Hints for Improving Nominations

1. Carefully review guidelines and state specifically (but briefly) how nominee stacks up
2. Emphasize impact/quality of nominee's contributions, e.g.
 - a. Effect of publications on targeted audience
 - b. Teaching awards
 - c. Innovations as Section or Chapter Chair
 - d. Evidence of leadership (and sustained work for profession)
 - e. Avoid over-emphasizing relatively routine contributions
3. Letters of support should provide added insights
 - a. Reflect breadth of nominee's contributions (e.g., letters

- from managers, customer, past students, journal editors)
- b. Need not (all) be from statisticians
- c. Base on personal experience (don't just repeat info on nomination)
- d. Stress value of contributions

Key question: How did nominee make a difference?

Hints on Preparing a Nomination for ASA Fellow

Robert R. Starbuck

1. A nomination package must be assembled and submitted to the Chair of the Committee on Fellows. Because the package will take some effort to prepare, the person preparing the package must be motivated and committed to completing the task.
2. It is recommended that the person submitting the package be an ASA Fellow, or that an ASA Fellow be added as a co-author of the package if the primary preparer is not a Fellow. The ASA home page provides a list of all ASA Fellows.
3. The deadline for submission of the nomination package is 1 March. To meet this deadline, *begin the effort on the package at least 6 months in advance.*
4. Determine whether the person you wish to nominate for Fellow (nominee) is not already a Fellow. If not, verify that the nominee is a member of the ASA and has been for at least 3 years prior to the submission deadline of 1 March.
5. Check with the nominee to determine his or her willingness to be nominated. Though few would decline to support efforts on their behalf, some persons may choose not to be nominated.
6. Ask the nominee for a current curriculum vitae and names of persons who know the nominee well and could provide supporting statements.
7. Authors need to be recruited to supply supporting statements for the activities listed on the nomination form. They should focus on selected activities, and the assignments of activities to the authors should provide adequate coverage of the list of activities on the form. A supporting statement from the ASA Section(s) that the nominee is a member of is recommended, and statements from ASA Fellows are strongly advised. Keep the number of authors from the nominee's place of employment to a minimum. Optimally, 6 to 10 supporting letters should be included in the nomination package.
8. Give a deadline to the persons assigned to prepare supporting statements. Keep in touch with them periodically; regular contact is usually necessary to insure that the statements are received on time.

Using your knowledge of the nominee and the information in the supporting statements, prepare a high quality presentation that will convince the members of the Committee on Fellows that the nominee deserves to be an ASA Fellow. Be sure to include the key points from the supporting statements. Make the presentation visually appealing, e.g., use a letter quality printer and a suitable font. Have your presentation reviewed and commented on by at least one other person.

Planning for the '99 ENAR Spring Meeting and the Joint Statistical Meetings

Christy Chuang-Stein

First, I want to thank our Section members for your great responses and support in planning Biopharmaceutical sessions at this year's ENAR Spring Meeting and the Joint Statistical Meetings. Without your active participation, the Section wouldn't be where it is today.

The ENAR Spring Meeting this year will be held in Atlanta on March 27 through 31. The ENAR Meeting traditionally offers a wide range of statistical topics and applications to various research fields and this year is no exception. At the '99 ENAR Spring Meeting, the Biopharmaceutical Section will sponsor 3 invited sessions. The first session is on "The Use of Computer Intensive Methodology in Drug Development - Using the Tools You Have to Answer the Question You Really Care About." This session, focusing on real examples from drug development in basic research, preclinical development, and clinical trials, illustrates how the availability of large computer capabilities has allowed statisticians to tackle some previously intractable problems. The second session, featuring "The Use of Meta-Analysis in Treatment Evaluation and Drug Development," will discuss the use of meta-analysis to draw inference in the evaluation of treatments. The session will

examine the role of meta-analysis in the drug approval process from the perspectives of the academia, the FDA, and the industry. It will also examine other issues related to meta-analysis such as bias propagation and the challenge of multiplicity. The third session addresses "Multiplicity Issues in FDA Submissions." This session includes 3 presentations on interim analysis and hypothesis generation in medical device trials, data-based (Bayes) adjustments for multiple comparisons, and correspondence between Bayesian and Frequentist methods in handling multiplicity issues in the analysis of drug experiments. The three presentations will then be followed by a discussion led by an FDA statistician.

There is also a contributed paper session at the ENAR Spring Meeting that could be of great interest to our Section members. This contributed paper session presents papers ranging from strategies for bioequivalence testing and calibrating tests for drug dilution and disk diffusion to approaches for combination drug synergy assessment and adjusting for center effects in clinical trials. This session is currently scheduled for 8:30 to 10:15 A.M. on Tuesday, March 30.

As for this year's Joint Statistical Meetings (August 8 through 12) in Baltimore, the Biopharmaceutical Section will sponsor 3 invited paper sessions and multiple special contributed (topic) and regular contributed sessions. The three invited sessions are: "Future Developments in Medical Statistics and Statisticians," "A Report on the Activities of the Adverse Events Working Groups," and "Sample Size Estimation in Clinical Trials." These topics were identified from a survey that the Section conducted among its members a while ago.

At the Joint Statistical Meetings, our Section will sponsor two 1-day short courses and a half-day workshop. The workshop, titled "An Overview of the Role of the Biopharmaceutical Statistician" by Bruce Rodda and Robert Starbuck, is for students and statisticians who are considering a career in the pharmaceutical industry. The first 1-day short course is on "Design and Analysis of Clinical Trials" by Jenpei Liu and Shein-Chung Chow and the second short course 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. The second short course is a new course designed for statisticians in the drug industry who have a moderate level of experience and who are dealing with phase II or phase III studies of new treatments. I would urge you to take note of this course and register early because space is limited.

In addition to the above short courses and workshop, our Section will also co-sponsor a short course titled "Designing and Implementing Economic Evaluations in Health Care" by Joseph Heys.

In a couple of months, all special contributed (topic) and regular contributed sessions at the '99 JSM will be finalized. Our Section will sponsor 8 special contributed sessions and an even greater number of contributed sessions. I will write to you about them in more detail later. All signs so far indicate that JSM '99 is going to be an exciting one with lots of fun and substance.

For right now, please mark down on your calendars March 27 through 31 for the ENAR Spring Meeting and August 8 through 12 for the JSM.

Biopharmaceutical Section Web Site

Kalyan Ghosh

The Web site of the Biopharmaceutical Section has been redesigned, reformatted and relocated. Among the changes, the most obvious is the look of the site, but perhaps the most important is the structure in which information is presented. Please take a look at this site, and send your comments or suggestions to Kalyan Ghosh, by E-mail: ghoshk@merck.com, or by telephone: (610)-397-7635. The URL for the new site is

<http://www.best.com/~asabp/>

As of now, the old site is still operational, where the only thing it displays is the URL of the new site indicating that our web pages have moved. For users whose Web-browser supports it, the old site takes them to the new location automatically after a few seconds. However, since the old URL will stop working altogether in the near future, be sure to change your bookmark to the new site.

Minutes of ASA Biopharmaceutical Section

Executive Committee Meeting— August 10, 1998, Dallas, Texas

Attendees:

Demissie Alemayehu	Sally Greenberg	Pat O'Meara
Tom Capizzi	Larry Gould	Phil Pichotta
Christy Chuang-Stein	Ralph Harkins	Bob Small
Bob Davis	Sandy Heft	Nancy Smith
Chuck Davis	Ken Koury	Steve Snapinn
Richard Entsuah	Jeff Meeker	Dave Stock
	Anne Meibohm	Ji Zhang

Ken Koury announced the winners of the 1998 elections for 1999 officers: Chair-elect Tom Capizzi, Secretary-Treasurer Sally Greenberg, Program Chair-elect Curtis Wiltse, and Council Representative Nancy Smith. He welcomed Nancy, who is new to the Executive Committee.

ENAR Meeting Minutes

The minutes of the March 31, 1998, meeting held at the ENAR meetings in Pittsburgh, Pennsylvania, were approved.

Treasurer's Report

Jeff Meeker reviewed the 1998 financial statement for January through June from ASA.

The Executive Committee voted to increase dues by \$2.00 to \$7.00 effective in 1999.

The Executive Committee also discussed three requests for funds. A request from WNAR to support a Young Researchers Luncheon at the 1999 WNAR meetings was rejected. A request for \$500 to support the 1999 Undergraduate Data Analysis Contest was approved. The Executive Committee also voted \$500 to support the 1999 Poster Competition.

Assignment: Jeff Meeker will inform Steve Porzio of ASA of the two contributions and the dues increase. He will also inform WNAR that we are not supporting their luncheon.

The members who attended the meeting for Section Treasurers discussed that meeting. Of concern was the September 30 deadline for a final budget and the threat to discontinue paying bills of those Sections who do not meet that deadline, since the Executive Committee usually does not approve the budget until the meeting in October. Jeff has informed Steve Porzio of this problem. Also discussed were some changes in the ASA staff organization. Nancy Hiatt is now Project Leader for Chapters and Sections.

Fellows Committee

Larry Gould reported the three nominees for ASA fellow put forward by the Biopharmaceutical Section were elected. He stressed that two of these three packages were not submitted by current ASA fellows. At the time of his report, he knew of a total of four new fellows from the Section (there

were several others). He had not made any progress on the intended improvements that he proposed at the Pittsburgh meeting.

Council of Sections

The Council of Sections met on Sunday, August 9. David Moore, ASA President, raised the question as to what Sections could do to meet better the needs of their Sections. He said that half of ASA members are not members of Sections.

Jonas Ellenberg, ASA President-Elect, reported for the Strategic Planning Committee. Council of Sections representatives were asked to take the eight goals to their Sections to discuss ideas of interest to them. The Board of Directors has provided \$100,000 in the budget for seed money.

John McKenzie, chair of the Constitution Committee, indicated a vote of the membership on the Constitution revisions would be this fall.

George Williams, chair of the Council of Sections Constitution Committee, indicated three changes have been proposed. Another suggestion was to require elected positions to have elections that are contested.

Sharon Anderson, a representative to the ASA Board of Directors, reported a mailing for a vote on the ASA Constitution revisions and a request for information to update the ASA Membership Directory would be made in September. She also reported that rates for JASA for 1999 will increase from \$32 to \$34 and rates for JBES will also increase. The Committee on Meetings proposed a four year rotation for future ASA meetings: 3 of 4 years would be in the northeast, north, or northwest; the fourth year would be in the southeast or southwest. Meetings will also be scheduled seven years in advance instead of the current five. She indicated Sections should be diligent in providing services to members: Sections who are not spending the money are not providing services.

Melinda McCann, reporting for Section Budgets and Fiscal Planning Committee, indicated the final budget is due September 30. She also asked what information Sections want, such as trends in Section membership over time (we already get this), who is attending meetings, list of new Section members, and a list of lapsed Section members.

COS Chair Linda Young indicated there will be an ASA membership drive this fall. She asked whether the Sections would be willing to give a free one-year membership to an incoming ASA member who specifies the Section as their primary Section. She urged Sections to make sure their web sites are up to date. She also raised the question as to whether the Section Web site should be put on the ASA server. The Executive Committee indicated it should not.

Linda Quinn requested Section support for the Poster and Project Competition.

The Council of Sections has started a Section of the Year Award, based on each Section's annual report.

1998 Joint Statistical Meeting Program

Tom Capizzi reported we have four invited paper sessions for JSM, one of which was obtained from the competition, four special contributed paper sessions, and eight regular contributed paper sessions. The session titles are in the

Pittsburgh meeting minutes.

The rule for special contributed paper sessions is that they will consist of 5 papers or 3 panelists. There is no limit to the number of special contributed paper sessions.

The Executive Committee discussed the allocation of invited paper sessions. While many factors go into the decision as to how many sessions a Section will have, one of the prime variables is the number of contributed papers that come from that Section. Based on this information, it was felt the allocation to the Biopharmaceutical Section was reasonable.

1998 Short Course

The Section-sponsored one-day short course Design and Analysis of Clinical Trials by J. P. Liu and Shein-Chung Chow was sold out with 44 attendees.

We discussed possibilities for 1999 short courses. Since the course this year was sold out, one option is to sponsor it again. Another proposal is the course previously given by Bruce Rodda and Bob Starbuck on an introduction to the pharmaceutical industry.

1998 Round Tables

Richard Entsuah reported the six round table discussions were sold out. Summaries are to appear in the Biopharmaceutical Report.

1998 Best Presentation Awards

Sandy Heft reported there are 12 sessions for which evaluations are being collected.

1998 Best Student Paper Awards

Ji Zhang reported 12 papers were submitted and five papers selected to receive the Best Student Paper Award, based on a blinded review of the papers by members of the committee:

- Anna Legedza, Harvard School of Public Health. *Prior Elicitation and Computation in Phase I Clinical Trials Using the Continual Reassessment Method*;
- Kewei Ming, University of Pennsylvania. *Substantial Gains in Bias Reduction from Matching with a Variable Number of Controls*;
- Charles Tan, Temple University. *MLE and M-estimator Based Approaches for Linear Statistical Relationship and their Applications in Assay Methods Comparison*;
- Catherine Tangen, University of Washington. *Complementary Nonparametric Covariance Methods to Proportional Hazards Regression in a Randomized Clinical Trial*;
- Brian Wiens, Temple University. *Testing Similarity of Three Binomial Proportions*;

Ji also provided an outline of the work required by the committee, including a time table and examples of the necessary communications.

Publications Committee

The following articles have appeared or will appear in *Amstat News*:

- October, 1997: *1997 Joint Statistical Meetings Summary* (Denise Roe);
- December, 1997: *FDA/Industry Interaction Workshop Summary* (Christy Chuang-Stein);
- January, 1998: *1997 Highlights* (Bob Davis), and *Student Paper Competition* (Denise Roe);
- February, 1998: *Invited Paper Proposals for 1997 ENAR Meeting and JSM* (Christy Chuang-Stein), and *Membership Benefits* (Phil Pichotta);
- April, 1998: *Biopharmaceutical Report* (William Huster);
- May, 1998: *Electronic Mailing List and Web Site* (Sally Greenberg), and *Announcement of Fall Workshop* (Bob Small);
- June, 1998: *1998 Joint Statistical Meeting Overview* (Tom Capizzi), and *1997 Best Contributed Paper Award* (Sandy Heft);
- August/September, 1998: *Winners of 1998 Best Student Paper Competition* (Ji Zhang);
- October, 1998: *Executive and Business Meeting Summary from 1998 Joint Statistical Meeting* (Jeff Meeker);
- November, 1998: *1999 Student Paper Competition Announcement and Procedures* (Student Paper Committee Chair);
- December, 1998: *Summary of Fall Workshop* (Bob Small);

The *1997 Proceedings of the Biopharmaceutical Section* are being printed. The press run size is 600 copies. The pre-publication price of the *1998 Proceedings of the Biopharmaceutical Section* will increase from \$18 to \$25, but otherwise the price will remain at \$25 for members and \$38 for non-members.

We invited speakers from the 1998 Midwest Biopharmaceutical Statistics Workshop to publish in the *1998 Proceedings of the Biopharmaceutical Section*. Response has been very slow, with only five authors expressing interest.

Biopharmaceutical Report

Anne Meibohm reported the second issue for 1998 of the *Biopharmaceutical Report* will be out soon. A third issue is planned. Copies of the first issue for 1998 were placed at the Council of Sections table.

Web Site

Sally Greenberg reported that with the exception of the Biopharmaceutical Report, the Web site is up to date. Two people have been identified as Webmaster and to redesign the web site: Kalyan Ghosh and Laura Hawthorne. The Web site will move to the same server as the mail list.

Electronic Mail List

Sally Greenberg indicated there are currently 127 subscribers. Sally will remain as mail list supervisor. Sally proposed a Policy for Search Firm Advertising on the Biopharmaceutical Section Electronic Mailing List. With a few minor changes, the Executive Committee adopted the policy.

Membership Committee

Phil Pichotta reported that as of July 1, there were 1954 members in the Biopharmaceutical Section. He indicated he is sending welcome letters to new Section members. He is beginning to address the issue of benefits for corporate members. He encouraged Section members to complete the forms for the update of the ASA membership directory. He also proposed we consider some way of celebrating the 20th anniversary of the Biopharmaceutical Section in 2001.

Midwest Biopharmaceutical Statistics Workshop

Pat O'Meara reported the 21st Midwest Biopharmaceutical Statistics Workshop was May 18–20, at Ball State University in Muncie, Indiana. The focus was computer intensive methodologies. Peter Westfall gave the opening plenary session on Applications of Resampling Methods in the Pharmaceutical Industry. Ray Myers' banquet speech "The Unique Aspects of the Statistical Profession" was entertaining and informative. Attendance was 178. Ten students, assisted by grants from Trilogy Consulting Corporation and G. D. Searle, attended the meeting.

Frank Shen will chair the 1999 meeting, which will be May 24–26 in Muncie. George Millikin will give the plenary talk. The three co-chairs are Gordon Pledger for Clinical, Mike Lutz and Edith Senderak for Non-clinical.

Deming Applied Statistics Conference

Dave Stock reported the Applied Statistics Meeting will be held in Atlantic City, December 7–11. The meeting will consist of tutorials on December 7–9 and short courses on December 10–11. A Web site for the conference has been established and a link to that web page from the Biopharmaceutical Section's web page has also been established. Copies of the program are available. Phil Pichotta provided the Section's mailing list for publicizing the conference.

PhRMA

Liannng Yuh reported the PhRMA Statistics and Data Management Workshop will be November 9–11 at the Hyatt Regency Hotel in Bethesda, Maryland. The theme of the workshop is "Opportunities and Challenges for Industry and FDA." Topics will include Genomics, Single Trial Strategy, and Data Mining. Liannng is overall Program Chair, and Ken Koury is the Clinical Program Chair.

1999 Joint Statistics Meeting

We were tentatively allocated three invited sessions at the

1999 JSM. Proposals include:

- *Progress of Adverse Events Working Groups*, Noel Moeberg;
- *Sample Size Estimation in Clinical Trials*, Phil Pichotta;
- *Future Developments in Medical Statistics and Statisticians*, Larry Gould.

Two additional sessions will be submitted in the competition:

- *Practical Experience in Using Multiple Imputation Method (with Solas) for Handling Missing Data/Dropouts in Clinical Trials*, Joe Shih;
- *Approaches to Incorporate Longitudinal Measurements as a Predictor for Outcome*, Gail Tudor.

Three special contributed paper sessions are being considered:

- *Dose Proportionality and Linear Pharmacokinetics*, Tom Bradstreet;
- *Clinical Trials Simulation*, Hng-ir Li;
- *Statistical Issues in Biotechnology and Vaccine Development*, Jim Whitmore.

There are also two proposals for invited poster sessions:

- *Analysis of Incomplete Quality of Life Data*, Ilsoon Yang and Lillian Mellars;
- *A Proportional Means Regression Model for the Cumulative Duration of Recurrent Events*, Steven Butler and Maja Paylic.

1999 ENAR program

ENAR tentatively allocated three invited paper sessions to the Biopharmaceutical Section for 1999. The three proposed sessions, with the organizers are:

- *The Use of Computer Intensive Methodology in Drug Development—Using the Tools You Have to Answer the Question You Really Care About*, Sandy Heft;
- *Statistics in Genomics and Bioinformatics*, Tom Vidmar
- *The Use of Meta Analysis in Treatment Evaluation and Drug Development*, Sue Marcus.

Post-meeting note: The second session has significant overlap with other sessions in the proposed ENAR program.

1998 Joint Biopharmaceutical Section/FDA Workshop

Bob Small reported the program has been finalized and an announcement appeared in the June *Amstat News*. The workshop will be held in Crystal City. Currently, there are 50 registrants. A reminder will be posted to the Section's e-mail list.

1999 Workshop

Bob Small indicated the workshop will again be joint with the FDA. One topic suggested was meta-analysis. Another

suggestion was to look at this year's round table luncheons for possible topics. Nancy Smith will be the FDA co-chair; one is needed from the Biopharmaceutical Section. Ralph Harkins and Bob Small will be members of the program committee.

Section Officer Election Slate

Bob Davis announced the following slate for 1999 elections:

- Chair-elect: Jeff Meeker, Bristol-Myers Squibb; Bob Small, Duke University;
- Program Chair-elect: Naitee Ting, Pfizer; Keith Soper, Merck;
- Council of Sections Representative: Ralph Harkins, Quintiles; Ji Zhang, Merck.

Executive Committee Appointments.

Ken Koury reviewed the appointments that have to be made and those that have been made so far:

- Executive Committee (1999-2001);
- Membership Committee (1999-2001)—new chair;
- Liaisons—Muncie—Frank Shen;
- Deming Applied Statistics—Dave Stock;
- PhRMA—Liannng Yuh (appointment made by PhRMA);
- Continuing Education (1999)—Bob Small;
- Finance Committee (not active);
- Work Group Coordinator (1999);
- Associate Editor, Biopharmaceutical Report—(1999; editor—2000; past editor, 2001);
- Webmaster (1999)—Done;
- Electronic mail-list moderator (1999)—Sally Greenberg;
- Fellows Committee (1999);
- Student Paper Committee (1999).

The appointments should be made by the fall meeting.

New Business

The fall transition meeting will not be held with the workshop, but will be held sometime in October somewhere in the northeast. It should be held near to a major airport.

Assignment: Ken Koury will arrange the meeting.

Phil Pichotta suggested the Section provide some form of recognition to ASA staff members who have been particularly helpful to the Section. The proposal was approved by the Executive Committee.

Minutes of ASA Biopharmaceutical Section Business Meeting

August 11, 1998, Dallas, Texas

Ken Koury welcomed the Section members and guests and introduced the current elected Section officers and the four newly elected officers for 1999: Chair-elect Tom Capizzi, Secretary-Treasurer Sally Greenberg, Program Chair-elect Curtis Wiltse, and Council of Sections Representative Nancy Smith.

Activity Review

Ken reviewed the many Section activities for 1998:

- The Section programs at the Joint Statistics Meetings and ENAR;
- The Best Contributed Paper Awards;
- Student Paper Awards;
- Fall Workshops;
- 1996—Adverse Events;
- 1997—FDA and Industry—Working Together to Expedite the Development of New Pharmaceutical Products;
- 1998—The FDA and Industry on Current Statistical Issues;
- Based on the 1996 workshop, a working group on Adverse Events was formed. That group will report at the 1999 JSM;
- ASA Fellows Committee;
- The organization of a Communications Committee to coordinate the Biopharmaceutical Report, articles submitted to Amstat News, *Proceedings of the Biopharmaceutical Section*, and the Section's Web site and E-mail list;
- This year's Proceedings of the Biopharmaceutical Section will contain papers submitted from ENAR and the Midwest Biopharmaceutical Statistics Workshop;
- Three issues of the *Biopharmaceutical Report*;
- Web site and electronic mail list;
- Membership Committee.

Treasury Report

By the end of 1997, the Section had reduced its cash-on-hand to \$49,160.51, thereby reaching our target. During the first six months of 1998, we showed a surplus of \$501.19, producing cash of \$49,661.70 as of June 30.

The Executive Committee voted to increase dues by \$2.00 to \$7.00 for 1999. This will put us in line with other Sections. Of the \$7.00, \$1.00 goes to ASA to cover administration and the remaining \$6.00 goes to the Section.

1997 Best Presentations of a Contributed Paper Award

Sandy Heft presented the awards for the Best Presentation of a Contributed Paper Award for papers presented at the 1997 Joint Statistical Meetings. The winners were:

- First Place: Devan V. Mehrotra, *ANOVA with Unequal Variances—Correcting a Popular Strategy*;
- Second Place: Joseph F. Heyse and Joseph G. Pigeon, *A Cautionary Note About Assessing the Fit of Logistic Regression Models*;
- Third Place: Ronald W. Helms, *Baseline Values are Random, Too: Using Baseline in Mixed Models*.

1998 Student Paper Competition Award

Ji Zhang presented the winners of the 1998 Student Paper Competition Award, in alphabetical order, with their plaques and checks:

- Anna Legedza, Harvard School of Public Health. *Prior Elicitation and Computation in Phase I Clinical Trials Using the Continual Reassessment Method*;
- Kewei Ming, University of Pennsylvania. *Substantial Gains in Bias Reduction from Matching with a Variable Number of Controls*;
- Charles Tan, Temple University. *MLE and M-estimator Based Approaches for Linear Statistical Relationship and their Applications in Assay Methods Comparison*;
- Catherine Tangen, University of Washington. *Complementary Nonparametric Covariance Methods to Proportional Hazards Regression in a Randomized Clinical Trial*;
- Brian Wiens, Temple University. *Testing Similarity of Three Binomial Proportions*.

Fall Workshop

Bob Small reported the FDA and Industry Workshop on Current Statistical Issues, Drugs, Biologicals, Medical Devices, and Risk Assessment, sponsored jointly with the FDA, will be held on September 24–25 at the Hyatt Regency Crystal City, Arlington, Virginia.

Fellows Committee

Larry Gould reported he knew of four members of the Biopharmaceutical Section who were to become fellows (there were several others). He stressed that two of the nomination packages were submitted by individuals who were not fellows.

He also reported the ASA Fellows Committee would be changed to consist of nine members appointed for three year terms.

1998 Joint Statistical Meeting Review

Tom Capizzi, 1998 Section Program Chair, reviewed the Section's activities at the Joint Statistics Meetings. We spon-

sored a one-day short course: Design and Analysis of Clinical Trials by J. P. Liu and Shein-Chung Chow. We organized four contributed paper sessions: "Statistical Issues in Vaccine Clinical Trials" (Brian Wiens and Tony Lachenbruch), "Evaluation of Statistical Procedures in the U. S. FDA Guidance for Bioequivalence Studies" (J. P. Liu), "Design of Phase I Trials" (Bill Rosenberger), and "Permutation Tests in Clinical Trials" (Vance Berger) and four special contributed paper sessions: "Statistical Issues in the Evaluation of Health Related Quality of Life," "Statistical Issues in Therapeutic and Diagnostic Devices," and "Statistical Methods for Incomplete Data I and II." In addition, we had eight contributed paper sessions and six round table discussions.

Deming Conference

Dave Stock reported the Deming Conference (Applied Statistics Meeting) will be held in Atlantic City, December 7–11. The meeting will consist of tutorials on December 7–9 and short courses on December 10–11. A web site for the conference has been established, and a link to that Web site from the Biopharmaceutical Section's Web site has also been established. Copies of the program are available.

Section Internet Activity

Sally Greenberg reported Kalyan Ghosh and Laura Hawthorne will be the Section Webmasters. By January, they expect to have a reformatted Section Web site.

The electronic mail list now has 127 subscribers. The Executive Committee voted to allow advertising of positions by recruiters under very controlled conditions.

Membership Committee

Phil Pichotta, Membership chair, reported the Biopharmaceutical Section now has 1954 members. He indicated each Section member attending the JSM was to receive a sticker for their badges in their registration package indicating their Section membership. He also reported he plans a membership drive this fall.

1999 Meetings

Ken Koury reported for Christy Chuang-Stein that we have three sessions for 1999 ENAR:

- *The Use of Computer Intensive Methodology in Drug Development—Using the Tools You Have to Answer the Questions You Really Care About*, Sandy Heft;
- *Statistical Issues in Bioinformatics and Genomics*, Tom Vidmar;
- *The Use of Meta-analysis in Treatment Evaluation and Drug Development*, Sue Marcus.

For 1999 JSM, we were allocated three invited paper sessions:

- *Sample Size Estimation in Clinical Trials*, Phil Pichotta;
- *Future Developments in Medical Statistics and Statisticians*, Larry Gould;

- *A Report on the Activities of the Adverse Events Working Groups*, Noel Mohberg.

We have entered two more in the competition:

- *Practical Experience in Using Multiple Imputation Method (with Solas) for Handling Missing Data/Dropouts in Clinical Trials*, Joe Shih;
- *Approaches to Incorporate Longitudinal Measurements as a Predictor for Outcome*, Gail Tudor.

Currently we have two invited poster sessions and two special contributed paper sessions. She needs volunteers to chair contributed paper sessions.

Anyone with ideas for sessions for 2000 ENAR or invited paper sessions for 2000 JSM should contact Curtis Wiltse.

Nominations Committee

Bob Davis, chair of the Nominations Committee, announced the nominations for 1998 Biopharmaceutical Section elections:

- President-elect: Jeff Meeker, Bob Small
- Program Chair-elect: Naitee Ting, Keith Soper
- Council of Sections Representative: Ralph Harkins, Ji Zhang.

New Business

An open meeting of the ASA Fellows Committee was announced.

Ralph Harkins and Nancy Smith are 1999 Section Workshop co-chairs. They invited program suggestions.

Biopharmaceutical Section Membership Passes 2000

Phil Pichotta
Membership Chair

As of February 16, 1999, there were 2048 members in the Biopharmaceutical Section, making us the second largest section in terms of membership behind the Statistical Computing Section. There are many more potential members out there, and I encourage you to invite your friends and colleagues to participate in our activities and to join the Section. Instructions about how to help with our membership drive are listed on our Section Web site: www.best.com/~asabp/. A few minutes of your time would be appreciated.

I review the membership list frequently and have become familiar with a lot of names. Do you know what the most common last name in our Section is? By far, the most common name is Wang with 28 members.

While this is just a bit of trivia, every member is unique and a valued member of our Section. Your input on the services provided by the Section and participation in activities is needed and appreciated.

Biopharmaceutical Section Roundtables

Joint Statistical Meetings 1998, Dallas

Dealing with Dropouts in Clinical Studies

Leader: William Myers, The Procter & Gamble Company

Participants in this roundtable were from the pharmaceutical industry, medical research centers and consulting companies; the majority worked within the pharmaceutical industry. A list of issues and methods of analysis was provided at the beginning of the roundtable in order to foster discussion. After introductions, participants discussed their experience (or lack of) in dealing with dropouts in clinical studies; the level of experience and knowledge was quite varied. A couple of interesting points were made during the initial comments. One participant said that he had heard the rule of thumb is that if less than 70% of the data are available then the study is flawed. A second participant mentioned the following quote from Don Rubin: "The proportion of missing data is not equal to the proportion of missing information". In other words, the proportion of missing information is usually less than the proportion of missing data. Another individual shared an experience, where the FDA performed a "worse case analysis" on the sponsor's data. The assumption was that all patients on placebo who dropped out of the study survived and were considered cured, while all patients on active treatment who dropped out of the study were considered treatment failures. There was agreement among the group that this approach was too conservative and that even the smallest dropout rate in the active group would most likely prevent demonstrating superiority over placebo for a truly effective treatment.

The first issue we discussed involved design considerations in order to mitigate patient dropout rates. There was a consensus that sponsors must be very proactive with study sites. In addition, variables that could potentially impact the likelihood of a patient dropping out of a clinical study must be collected. These variables could be used to compare patients who dropout with those who complete the study. Several additional design considerations that have been discussed in the literature were mentioned. One involved the use of a non-randomized trial period where all patients receive active therapy for a period of time; those patients free of side effects would then be randomized to either active or placebo. Most of the participants were not in favor of this, because it was felt that the study objective and patient population would be altered. The second design consideration involved tightening the inclusion/exclusion criteria in order to reduce dropout rates. The majority at the table were not supportive of severely tightening the inclusion/exclusion criteria. Finally, it was also pointed out that if the event rate is of primary interest, then extending patient follow-up to compensate for dropouts will help address a loss of statistical power. However, it will not handle the problem of potential bias.

We discussed methods for determining if patients who complete the study are a representative sub-sample of the original patient sample, i.e., address potential bias. The most widely discussed method was to compare dropouts versus completers with respect to baseline variables. If no significant differences are found, then there is evidence that the completers are a representative sub-sample. It was also mentioned that one should compare the frequency of and reasons for dropout between treatment groups.

Several methods (complete-case analysis, last observation carried forward (LOCF), unconditional or conditional mean imputation, and multiple imputation) for analyzing data when dropouts (missing data) are present were reviewed. These methods are used for longitudinal and/or single end-point studies. The complete-case analysis was not looked upon favorably, because of potential bias and loss of statistical power. There was a consensus that the LOCF method should not be implemented from a statistical perspective. Yet several participants were aware of studies where the method had been used. One individual recalled that there are still some regulatory guidelines that recommend the LOCF method. One of the participants mentioned that they had reasonably good success with mean imputation methods. However, it was pointed out that with mean imputation, the variance is underestimated. The method that received much of the discussion was multiple imputation. In short, this method replaces each missing value with two or more values drawn from an appropriate distribution of the missing values (multiple imputations are repeated draws from the predictive distribution of missing responses). This results in two or more complete data sets, each of which is analyzed using the same standard method. The analyses are then combined in a way that reflects the extra variability. The multiple imputation method is superior to single imputation with regard to validity of interval estimates and significance level. One participant mentioned that their company had used multiple imputation for an NDA submission. He said that their group worked very closely with the FDA on the implementation of the method and that this particular division was very receptive to the idea. Solas, a software that can perform multiple imputation methods as well as many other methods for missing data, was briefly discussed. For longitudinal data, likelihood based methods (e.g., PROC MIXED) were a top choice for many of the participants. Generalized estimating equations for binary data, count data, etc. was also proposed.

At the end of the discussion several other methods were mentioned as viable options in order to handle dropouts. There are methods in the literature that convert outcome variables into ranking of patients based on desirability of outcome (Gould, 1980; Pledger and Hall, 1982). For example, those patients who withdraw because they are cured will get the highest rank, while those who withdraw for intolerance or lack of benefit will receive the lowest rank. These methods follow the intention-to-treat paradigm. An alternative method (Shih and Quan, 1997) is a composite approach where the outcome variable is continuous and the response at the end of the study is of interest. The analysis addresses a two end-point problem when comparing two treatments. The first is the discrete probability of dropping out of the study, and the second is the continuous conditional mean of completers. These two endpoints formulate a joint hypothesis. Because of

limited time there were several other methods that were not discussed (a weighting method—Heyting et al., 1992; Brown, 1992; a nonparametric randomization technique—Entsuah, 1996; implementation of summary measures and meta-analysis—Talwalker, 1996). In summary, all the participants felt that additional discussion and research were needed in this particular area. Some of the issues are philosophical and others are more technical. This would pertain to both study design and data analysis. It was also felt that many of these methods are not rivals, but rather address different questions. In other words, they complement one another. This leads to the belief that in most cases, several analyses should be performed in order to completely understand the true treatment effect, i.e., perform sensitivity analyses. One participant summed it up well when he said “It is nice to know that I am not the only one having trouble dealing with this issue and that there does not appear to be a golden bullet”.

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Statistical Analysis in Outcomes and Pharmacoeconomic Studies

**Leader: Christopher M. Barker, Roche
Pharma Business—Palo Alto**

The luncheon roundtable theme concerned the opportunities and challenges presented by the inclusion of pharmacoeconomic objectives in clinical trials of new treatments. The participants at the roundtable included statisticians from the pharmaceutical industry as well as academic researchers

and statisticians affiliated with medical centers or hospitals. The responsibilities of the attendees ranged from clinical trial design to measurement of outcomes in hospital settings and assessment of hospital charges (or costs). The role of pharmacoeconomics is likely to grow because pharmaceutical and health care purchasers (e.g., HMO's or government budget authorities) use not only safety and efficacy of new drugs but also pharmacoeconomic evaluation when deciding to provide reimbursement or to provide a formulary listing. Pharmacoeconomic analysis of a clinical trial often involves the integration of efficacy, safety and quality of life and concepts less well known in biostatistics such as measures of patient "utilities" for various health states and combining these with measures of resource utilization such as direct and indirect costs. One topic for continued research is selecting the best utility assessment method. Other topics include selection and validation of QoL instruments, definition of an "effect size" when computing sample size for studies involving QoL, and analysis of cost data. Roundtable members appeared to reach a consensus that further discussions of these subjects at future meetings of the ASA are appropriate.

Let's Hear from You!

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