Biopharmaceutical Section

American Statistical Association

Biopharmaceutical Report

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Chair: *Leonard Oppenheimer* **Editors:** *Demissie Alemayehu, David Giltinan, and Kevin W. Anderson*

Note from the Editors

In this issue of the *Biopharmaceutical Report*, R. Davis, M. Free, S. Gulyas, M. Hearron, S. Lindborg, R. O'Neill and C. Sampson give a detailed and illuminating account of the history of the Biopharmaceutical Section for the period 1966 through 1988. The report traces the evolution of the section from an informal group in the mid-1960s to its present status as the largest of the 22 sections of the American Statistical Association. The article pays homage to the early pioneers who led the charge in the formation of the section, and documents the successful collaboration between government and industry statisticians in defining the vision and identity of the section. While the complete text with appendices can be found on the Biopharmaceutical Section website, we trust the material presented in this issue will serve as an interesting and valuable resource to members of our profession. ■

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Letter from the Chair

Leonard Oppenheimer

Since it's the season of Inaugural and State of the Union speeches, let me join the fray, as I begin my year as Chair of the Biopharmaceutical Section. The State of the Biopharmaceutical Section is excellent and getting better. We are currently the largest section of ASA and would like to increase our membership further (more on that later). We have sponsored excellent scientific programs at ENAR and JSM thanks to our current program chair Kannan Natarajan. At the JSM meetings in August, 2005, we will sponsor 8 Invited Sessions, 8-10 Topic Contributed Sessions, over 20 Regular Contributed Sessions, 13 Luncheon Roundtables, and 3 Continuing Education Courses.

Our Fall FDA/Industry Workshop (co-chaired by Ji Zhang and Steve Wilson) was quite successful in generating thoughtful discussions among industry, academics, and regulators on cutting edge topics (see Ken Koury's excellent summary later in the *Report*). Attendance at this meeting has been increasing exponentially and was just over 500 attendees this past fall. Our financial situation is excellent thanks to our Corporate Sponsors (Corporate Sponsor Committee: Brian Wiens-Chair; Kay Larholt, Russ Helms, Jim Colaianne), the financial success of the FDA/Industry Workshop, and the fact that our Continuing Education courses draw well. We have an active and committed membership volunteering their time and talents to help the section (check out the website to see many of them listed). This is a section where the position of chairperson is the easiest job of all.

So what would I like to work on during my one-year tenure? Since everything is going well, and nothing is broken, we are talking about "continuous improvement" and enhancing the value that our section can provide to members. I would like to increase our membership even more since I'm sure that many of your co-workers are not members of our section, and perhaps not even members of the ASA. Avital (Tuli) Cnaan and Mike Hesney are co-chairing a committee to help identify these individuals and to try to convince them to join. We will need your help in this effort. You'll be hearing more from Tuli and Mike on their plans for increasing section membership.

I would also like to begin developing ideas as to how we could best exploit our positive financial situation to best help our members – whether it's more support to students, to helping promote the proper use of statistical science to benefit society, to enhancing our continuing education and professional meeting opportunities. If you have ideas or suggestion that you would like the Executive Committee to consider, please send them to me.

Check out our website to see what's going on and who to contact – there's a lot of activities. Christie Clark is our program chair in 2006 – it's never too early to start thinking about sessions or continuing education or roundtable luncheons. Ken Koury and Mary Bartholomew are our FDA/Industry Workshop co-chairs for this fall's meeting. Demissie Alemayehu is our *Biopharmaceutical Report* editor if you'd like to contribute an article. If you'd like to nominate a deserving colleague to be an ASA Fellow- talk to Tuli Cnaan. If you'd like to become more involved in the many activities of the section, drop me a note. We can always use more helping hands.

I look forward to getting your ideas and suggestions on how the section can better serve its members and the statistics profession. ■

The History of the Biopharmaceutical Section of the American Statistical Association (ASA), 1966-1988

Robert L. Davis, Retired, AstraZeneca
S. Michael Free, Retired, SmithKline Beecham
Stephen W. Gulyas, Pfizer Inc.
Martha S. Hearron, Retired, Pharmacia and Upjohn
Stacy R. Lindborg, Eli Lilly & Company
Robert O'Neill, U.S. Food and Drug Administration
Charles B. Sampson, Retired, Eli Lilly & Company

Executive Summary

The Biopharmaceutical Section of the American Statistical Association (ASA) has a rich history. The Section began as an indirect result of the various Congressional acts in the 1960s and beyond to mandate the conduct of clinical trials. The roots of the Section go as far back as the mid-1960s. Although the Section was first established as an informal group, interested parties quickly organized and grew into a subsection of the Biometrics Section of the American Statistical Association (ASA). Gatherings of this early group piggybacked onto meetings such as the Midwest Biopharmaceutical Statistics Workshop (MBSW), the Eastern North American Region (ENAR) of the International Biometric Society (IBS), and the Princeton meetings. As the subsection gained more prominence within statistical circles, the subsection desired to break off into a full Section. There was some opposition to the newly proposed Section, but in the end, full-section status was granted.

Today, the Biopharmaceutical Section is the largest of the 22 Sections currently within the ASA. It contains over 2000 members, sponsors a variety of conferences, and is a consistently large contributor to many conferences. With the expected growth of the healthcare field during the 21st century, the ASA Biopharmaceutical Section is well positioned to support statistical issues germane to the pharmaceutical industry for years to come.

1. Introduction

Since its inception in 1849, the American Statistical Association (ASA) has seen a variety of applications to the fields of biology and healthcare. From agriculture to genetics, the ASA has provided a forum for the advancement of statistical knowledge.

A series of government actions beginning in the 1960s set the stage for a new branch of statistics. The infamous thalidomide disaster, where babies experienced a higher risk of serious birth defects from the medicine taken by their mothers while pregnant, sparked tighter governmental oversight for the advancement of new medicines. The passage of the Harris-Kefauver Act (1962)[1] mandated that all new medicines must establish both safety and efficacy through the use of adequate and well-controlled clinical trials; later, previously marketed medicines also had to meet these requirements. This first regulatory requirement ensuring a strict process for the development of a new medicine had an expectedly large effect on the pharmaceutical industry. It pressed research divisions in pharmaceutical companies to hire additional analytical staff to help develop new methodology for the scientific collection, evaluation, and presentation of research data. It was also responsible for a new surge of almost secure employment for statisticians in the biopharmaceutical area across the industry, academia, consulting, and government. Some companies hired statisticians from academic departments to set up the necessary statistical support within their companies. However, the statisticians they were able to hire were mainly recently graduated statisticians, with limited experience in the healthcare field. There were virtually no medical schools that contributed statisticians to the field at the time.

2. Early Days

With the surge in hiring in the pharmaceutical industry, these newly hired individuals sought a respected professional venue for technical and developmental support in this new field. Such an independent group could help develop new methodology, stimulate universities to include new curricula

associated with biopharmaceutical research, help recruit new specialists in the field, and obtain additional sessions at the annual ASA meeting. The concept of a formal pharmaceutical industry-oriented interest group was first discussed at the ASA meetings in Los Angeles during the summer of 1966. A group that included Joe Meyer (Merrell), Charles Dunnett (Lederle), Stu Bessler (Syntex), Bob Assenzo (Upjohn), Marti Hearron (Upjohn), Ron Gauch (Ciba-Geigy), Joe Dresner (Parke-Davis), Joe Ciminera (Merck), Bob White (Hoffman-LaRoche), and Charlie Redman (Eli Lilly) informally discussed the possibility of creating a venue whereby pharmaceutical industry statisticians could share their common issues. The committee circulated some material based upon their first discussion and then asked for names of people who would be interested in joining the group.

At the annual ASA meeting, the group set out to determine if there was broader interest among the statistical community by posting a hand-written petition on the ASA Meeting's Bulletin Board. Having the proper equipment at hand (a pen and paper!), Joe Dresner was drafted to compose the petition, survey the interest, and then report back to the group. After only one day of posting the petition, approximately 50 signatures were received. In addition, he received many direct phone calls indicating a strong interest in forming such a group. He received very few negative responses, mostly from members of the ASA Biometrics Section Council who felt that the existing Biometrics Section adequately served the stated needs. Joe Dresner reported back that there was a pleasantly surprising overall interest in the initiative.

There was an open question as to which professional affiliation would best serve this new interest group. A small group of leaders emerged from this group and were called the Pharmaceutical Steering Committee (PSC). They identified the ASA as one of the possible organizations that might house this group; others that were considered were The International Biometrics Society (IBS), The American Society for Quality Control (ASQC), The American Association for the Advancement of Science (AAAS), and the fledging Drug Information Association (DIA). Responses from the original survey were also reviewed by the PSC to see where individuals might prefer the group to seek affiliation. The PSC also noted that the ASA had a provision allowing for the formation of additional affinity subgroups, provided there was sufficient interest.

The PSC then had to determine the next steps for the infant organization. Joe Dresner informally met with key ASA figures, Sam Greenhouse and Marvin Schneiderman. The PSC received feedback that they should further survey for broader interest before formally approaching the ASA. Members of the Biometrics Section were approached about supporting a potential subsection. These individuals received the idea warmly, as they were already consulting about pharmaceutical issues and recognized this as a growing area of statistics. Shortly thereafter, the PSC mailed a survey out to potential members and received about 100 positive responses. In 1967, the PSC decided that the new group, to be called the Pharmaceutical Subsection, should join ASA as a subsection of the Biometrics Section, a decision greeted with enthusiasm at the ASA office. Ultimately, the PSC had felt that the statisticians should remain part of a focused, technical organization, rather than join a broad assortment of disciplines such as the DIA.

3. The Biopharmaceutical Subsection (BPSS)

Now with a solid group of proponents ready to support the organization, the PSC actively sought ASA subsection status. Joe Dresner, Charlie Dunnett, Mike Free, Ron Gauch, Marti Hearron, Joe Meyer, and others led the charge. These members of the PSC turned over the petitions to the Biometrics Section, who then submitted the formal request to the ASA Board in 1968. The Board approved immediately and thus, the first subsection in the ASA was created. Fittingly, this subsection was now a part of the oldest section of the ASA, the Biometrics Section.

It should be noted that there was no intention of becoming a full section at this time. This was just as well since the ASA was not very receptive to the establishment of new sections during this period. Many reasons for the Board's reluctance existed, including the fact that there were few sections within the ASA, a new section meant a lot of administrative work, and not many interest groups even existed within the ASA. Furthermore, the potential subsection members did not feel that there would be enough support to create an entirely new section from scratch.

The subsection chose its early leaders from among its pioneers. Joe Dresner was elected as the first chairman of the subsection; Joe Meyer was elected as the first secretary (Appendix B). The Pharmaceutical Subsection morphed in name into the Biopharmaceutical Subsection (BPSS) so that there would be no confusion with the Pharmaceutical Manufacturers Association (PMA, now known as PhRMA).

4. Growth of the BPSS

The newly created subsection quickly became a participant in various meetings. Concurrent with the newly granted subsection status, the BPSS was invited to present two technical sessions at the 1968 ASA Annual Meeting in Pittsburgh. Then, in December 1969, Joe Ciminera represented BPSS at the Princeton Conference was started by ASQC in 1945. The following year, the BPSS was granted a full session at the Princeton Conference, where several members presented. In 1971, the BPSS became a co-sponsor and regular participant at the Princeton Conference, which continues today as "The Annual Deming Conference on Applied Statistics", which has been subsequently held in Villanova, PA, Newark, and now Atlantic City, NJ. The BPSS found the Princeton Conference to be a convenient venue since this allowed the subsection to meet as a whole on a regular basis: at ENAR in the Spring, at the Joint Statisistics Meeting (JSM) in the Summer, and at the Princeton Conference in the Fall . Furthermore, the atmosphere at the Princeton Conference was conducive to discussing issues universal to the healthcare industry.

5. Pharmaceutical Industry and FDA Initial Interactions

By 1969, most of the pharmaceutical companies had statistics departments, the numbers of pharmaceutical statisticians had reached critical mass, and the amount of new hires into industry was increasing. However, most of the new industry statisticians were heavy on academic training, and had much to learn about the healthcare industry. There was a strong sentiment for these statisticians to become affiliated with a

respected scientific organization, such as the ASA, to defuse any possible suggestion of bias in their work.

Although the FDA was wrestling with similar issues as their fledgling industry counterparts, they also had to deal with internal policy concerns. Due to fears of being misconstrued as forming FDA opinion or appearing to compromise the independent regulatory process, FDA statisticians originally could not be active in any groups involving external organizations, such as BPSS or PMA. However, a policy change in the early 1970s at the FDA relaxed the rules to some degree. As they became more participatory in pharmaceutical statistics meetings, the primary professional statistical society they contributed to, and sought help from, was the BPSS. The BPSS actively extended invitations to FDA statisticians to participate/present in professional meetings. But even then, FDA statisticians were very strict about not providing comments or interpretations of any regulations.

As the FDA statistical program was developing to meet the regulatory challenges of the agency, Charles Anello, the new Director of the program, created an advisory committee in 1969 of statistical and epidemiologic experts to advise the FDA on how to set up an adverse event surveillance system. Dr. Anello was the first executive secretary of this Biometrics and Epidemiology Methodology Advisory Committee (BEMAC) which was also mandated with providing policy advice on many other issues of importance to FDA. Some of the early statistical members of this committee were Jerome Cornfield, Samuel Greenhouse, Marvin Kastenbaum, Harry Smith, John Gart, Marvin Zelen, Jacob Bearman, Curtis Meinert, Ron Helms, James Grizzle, Byron Brown, and Max Halperin. The BEMAC often met in conjunction with a FDA subject matter committee such as the Cardio Renal or Metabolic and Endocrine Committee when specific issue need statistical advice were pressing. The BEMAC committee served as the forum for statisticians from the pharmaceutical industry, and in particular from the BPSS to come before the committee in a public forum and make presentations on issues of importance to FDA and to pharmaceutical statisticians. One of the topics dealt with the need to assure the quality of data in clinical trials. Because of the conflict of interest rules, it was not possible for BPSS industry statisticians to serve on the BEMAC. The BEMAC existed for about seven years, being disbanded in 1977 in favor of a new allocation of each of the current statistical members being placed on each of the subject matter advisory committees as voting members.

The BPSS Executive Committee had been aware of this movement and sent an enthusiastic letter to FDA supporting the continuation of the BEMAC, but the BEMAC was disbanded during the Carter Administration as part of a larger government effort to reduce and streamline the number of external committees advising the government. As the value of statisticians to the advisory process was well understood and in some sense there was a trade of the concentrated advice provided by the BEMAC committee for a broader approach of disseminated advice, influence and impact of many statisticians as voting members on different subject matter committees. In response to FDA requests, the BPSS helped identify qualified committee members and continued to supply nominations to FDA for qualified candidates to sit on these committees. This served as the first general collaborative effort between the FDA and industry to solve common problems, and the first venue for counterparts to meet each other.

The BPSS effectively liaised with other key organizations in its early years and was able to focus attention on the areas of need for statisticians in the pharmaceutical industry. It successfully raised awareness and sparked discussion about technical issues that they faced regularly, including pharmacokinetics, clinical trials, protocol design, multi-center considerations, and sample size. The BPSS and its meetings provided a mutually beneficial forum for industry and FDA statisticians to talk and provided insight to the PMA on statistical methodology required in a regulatory environment. The PMA was very interested in collaboration given the newly regulated environment. Since they were the conduit for obtaining action from the FDA, as well as setting a higher standard for statisticians, members of PMA requested input from BPSS leaders about how best to do this. The BPSS was eager to participate, as they were concerned about how the FDA would function. The PMA also felt that they needed to meet with industry statisticians, even though there were no formal meetings at the time. Out of this exchange, the BPSS took an active role in joint FDA/PMA committees for the development of protocol guidelines for specific diseases by nominating industry statisticians to serve on these panels. Separate PMA groups met informally to discuss interactions with the FDA, and although BPSS was not directly involved, some members of BPSS did participate to provide statistical perspective that was previously lacking. These interactions led to the creation of the PMA Biostatistics Committee.

As part of the outreach and pro-active nature of the BPSS at this time, there were several new firsts for the young organization. In 1970, a small group of subsection members met to respond to the FDA Commissioner's publication on Controlled Clinical Trials. The meeting was in the office of Marvin Schneiderman at the National Institute of Health (NIH) and included Chuck Anello (FDA), Joe Ciminera (Merck), Bob Assenzo (Upjohn), Charlie Dunnett (Lederle), Mike Free (SmithKline), Bob Teichman (ICI), Joe Dresner (Parke-Davis), Joe Meyer (Squibb), and David Bray (Health Protection Branch, Canada). In an attempt to further thinking in two specific areas of general interest to subsection members, the BPSS Executive Committee identified two topics to be studied informally in 1971: 1) bioavailability, and 2) the enhancement of the process of statistical evaluation and review in NDA submissions. These discussion groups eventually evolved into "working groups" discussed later.

6. BPSS Maturation and Signs of Independence

The BPSS enjoyed the benefits and pains of steady growth during the 1970s. By the middle of the decade, the number of subsection members on the rolls totaled four figures, although less than 200 were noticeably active. During the timeframe of 1966-1979, the membership of the BPSS grew from 100 to approximately 1500. In 1972 and 1973, there was growing concern regarding limitations on technical sessions allocated to the subsection, as well as the size of the assigned meeting rooms for both the ASA Annual and ENAR meetings. After full-section status was achieved in 1980, the membership grew in the late 1980's.

The confluence of the increased contributions to the profession, frustration over meeting space, the sheer size of the membership of a subsection, and other concerns led to open discussion of the necessity to obtain for full-section status for the BPSS. However, the minutes showed that in 1975, the BPSS Executive Committee passed a motion to remain a subsection. The Executive Committee felt that it would not be wise to be vulnerable as an individual organization. However, at the BPSS business meeting later in 1975, unexpected support grew for the idea of obtaining full-section status. Support for this position came, in part, from members of the rank and file who may not have been fully clear on the ramifications of their decision; some members were confused about the organizational differences between the International Biometric Society (IBS) and the Biometrics Section of the ASA. Furthermore, many prominent statisticians were members of both organizations, but may not have been fully aware of the detailed business of either. In an abrupt reversal, action from the floor resulted in the appointment of a committee to consider full-section status.

The technical contributions of the subsection continued steadily into the second-half of the decade. At the ASA Annual meeting in 1976 in Boston, the technical session topics included "General Statistical Guidelines for Submissions to the FDA" and "Consequences of Testing Drugs for Carcinogenicity." A small group prepared a formal response to the FDA on the Statistical Guidelines and a Federal Register Notice on Good Laboratory Practices (GLP). Interest in public policy continued with a position piece that provided six essays on how to better use statistics in regulatory decisions.

Strategic planning vital to the BPSS' own advancement, and reminiscent of that which occurred 10 years earlier, again came to the forefront in 1976. Interest in full-section status was temporarily quieted by a Biometrics Section committee report that indicated the current leadership and activities reflect the need and interests of the active membership. Despite this brush-off, some of the BPSS membership were still agitating, albeit unsuccessfully, for full-section status. The Biometrics Section of ASA, however, was not paying much attention to the subsection as a whole, let alone to these intermittent calls for a split between the organizations. Consequently, the frustrations of the BPSS over the lack of meeting space and other issues continued to fester. This culminated in the last BPSS Executive Committee meeting of the year where a motion was passed supporting the statement, "The policy of BPSS, through its Executive Committee, should be to make every effort to attract academic and government people into the activities of the Subsection." In turn, this would indirectly bring the BPSS additional credibility, as well as make it painfully obvious that the subsection had its own distinct needs, in the eyes of the Biometrics section and the ASA as a whole. This initiative proved to be extremely fruitful, resulting in two key individuals from the FDA being subsequently appointed to the BPSS Executive Committee: Bob O'Neill (Clinical) and Bill Fairweather (Non-Clinical).

In 1977, BPSS prepared a response to the Federal Register Notice on Clinical Investigator Guidelines, which recommended having separate clinical and statistical reports. With the help of Bob Temple, Bob O'Neill, and Bob Assenzo, it was argued successfully that there should be one common report.

One of the positive changes in 1977 was the establishment of a new conference, which would have long-range planning ramifications for the BPSS. The Midwest Biopharmaceutical Statistics Workshop (MBSW)[2], affectionately known as the Muncie meetings, was begun by BPSS activists from the Midwest (Appendix C). This Conference was created for many reasons, not the least of which was to provide a forum for young biostatisticians who worked in the pharmaceutical industry or allied organizations to present their work and interact with more senior members of the broader statistical profession. Additionally, this provided an alternative midwestern response to the Princeton Conference hosted by ASQC. The Muncie meetings served as a venue for authors of the original Biopharm charter to meet and draft the document. The ASA Board wondered about the motivation for this Conference because they had been burned before by having to accept responsibility and debt for prior failed conferences. This concern eventually faded as sections and chapters obtained their own treasuries and solidified as organizations. Initially, there were no organizational connections between the BPSS (ASA) and MBSW other than the statisticians who participated in both organizations. But, eventually the descendants of BPSS would co-sponsor the MBSW and, in effect, provide many of the advantages that the ASA sponsorship would have itself provided.

More regulatory action ushered in the second decade of the formal BPSS organization in the late 1970's. There were continued repercussions of the Delaney Amendment, originally passed in 1958, which dealt with testing compounds for carcinogenic potential. This created a more formal research area which demanded the need for statistical input to solve new and interesting problems, including an expanded role into the pre-clinical arena. As more and more academic biostatisticians recognized the fertile field and wide variety of problems in this arena, more balance and credibility was added to the growing membership of BPSS.

7. The Road to Independence

Due to the ever-increasing size and scope of the subsection, momentum towards obtaining full-section status gained strength in 1978. Membership was steadily increasing, a Committee for Government Liaison was formed, contacts with scientific and medical journalists were initiated, and medical school statisticians and others also expressed interest in joining the subsection.

Additionally, the BPSS felt a yearning for a higher profile than a subsection. Leaders within the subsection felt there were potential fellows in the BPSS that were not being given proper consideration for nomination. Consequently, the BPSS Executive Committee discussed nominations for ASA fellows and submission strategies. There was also a desire to have additional influence in the running of the ASA. Finally, the BPSS was now a vibrant organization which was dealing with major national issues and was supported by a rapidly growing population of members.

Due to all of this stature, success, and sentiment, the BPSS Executive Committee began aggressively pursuing and strategizing for full-section status in late 1978 and early 1979. Charlie Sampson, Marti Hearron, and Kathleen Lamborn began a review of the original charter. Simultaneously, the group approached Fred Leone about the possibility of the BPSS receiving full-section status. Dr. Leone was extremely supportive and assisted the BPSS leadership in crafting a plan.

To begin, a clear description of the potential advantages of the section status was needed for the BPSS. Both the ASA and the parent Biometrics Section had to benefit. A statement of purpose, an expansion of the by-laws, and a new charter would be needed. BPSS defined its proposed scope to include non-government sponsored clinical trials, basic screening of drugs, and toxicology.

An equally integral component of Dr. Leone's plan was a strategy for gaining support from many committees and factions in the ASA, even though they naturally might be leery of such an initiative. With this advice, the BPSS chose a low-profile strategy in pursuing section status. Charlie Sampson received much resistance but pursued the cause relentlessly. A year and a half of hardcore lobbying and discussion led to strong support from many key figures within ASA. With the formal documentation and informal lobbying in hand, a series of committees had to be approached. A presentation was made to a new ASA Committee on Sections and Subsections and followed by a presentation to the ASA Committee on Committees.

But not everyone was willing to go along with the BPSS proposal. In particular, the Biometrics Section was not supportive and began a lobbying campaign to block full-section status right after the ASA Annual Meeting in 1979. The Biometrics Section's leadership was powerful politically and was highly regarded in the academic community. Because of this stature, the Biometrics leadership successfully raised concern about how a fair distribution of "interests" between the Biometrics Section and the proposed Biopharmaceutical Section would be created and subsequently maintained, whether each organization would cannibalize each others' topics on clinical trials, etc. Tension between the two organizations continued to increase and ultimately could only be resolved through the ASA Board of Directors.

In a letter dated January 3, 1980, members Drs. Koch and Zelen and key members of the BPSS were invited to present their case to the ASA Board of Directors (Appendix D). A letter was sent to H.O. Hartley laying out the rationale for full-section status and requesting to be placed on the agenda for the ASA Board of Directors (Appendix E). On February 1, 1980, in Washington DC, the Biometrics Section and the BPSS squared off with dueling presentations for and against full-section status for the BPSS (Appendix F). Margaret Martin presided over the meeting as current Chair, and H.O. Hartley (past Chair), and Ralph Bradley (Chair-elect) also served on the Board. The Boardroom was packed. It was not obvious if the room was too small or if there were too many guests invited to the meeting. Charlie Sampson and Carl Metzler made the presentation on behalf of the BPSS. Gary Koch, as Chair-elect of the Biometrics Section, made the presentation on behalf of the Biometrics Section since Marvin Zelen (Biometrics Chair) was unable to attend. After much passionate discussion with some rather discouraging remarks being made by a few Board members, Joe Fleiss, the ASA Board member representing the Biometrics Section, rose to speak. Fleiss said that the BPSS had shown much initiative, an activity level greater than the other current sections, and therefore it would be shame to deny this petition. That speech won the day, and Margaret Martin and H. O. Hartley closed out the discussion. The vote was taken, and the Biopharmaceutical Subsection had passed their greatest hurdle in becoming a SECTION. Thus, the new Biopharm Section became only the eighth in existence at ASA. This decision was announced formally to the BPSS group through correspondence from Fred Leone (Appendix E)

The accomplishment of that day was a fitting end to the long road the BPSS had to take in seeking full-section status. There were a number of political land mines which, in the end, the BPSS successfully navigated. Others who deserve a part of the limelight are Fred Leone, R. L. Anderson, H. O. Hartley, Margaret Martin, John Bailar, Marvin Schneiderman, David Blackwell, Sam Greenhouse, Paul Meier, Byron Brown, and Joe Fleiss. Additionally, there were many others who supported the application and are too numerous to mention, but deserve thanks nonetheless.

8. Defining New Paths

In stark contrast to the feverish and tense posturing prior to the Board of Directors presentation, the separation of interests between the two sections went smoothly. John Bailar and Marvin Schneiderman represented the Biometrics Section while Mike Free and Charlie Sampson represented the new Biopharmaceutical Section. It was agreed that clinical trials and pharmaceutical safety interests were Biopharmaceutical Section interests and agricultural applications, such as livestock and agronomy, should remain with the Biometrics Section. It was also agreed that the Biometrics Section would absorb a very active industry group interested in animal health studies and associated FDA submissions. Eventually, the scope and functions of the Biometrics and Biopharmaceutical Sections evolved into their distinct jurisdictions today as given in their Charters (Appendix G) and as first published in the 1985 Directory of Members, American Statistical Association.

Over the next few years, the Biopharmaceutical Section enjoyed its autonomy while growing into full-section status, yet continued to support technical programs and regulatory relationships. The year 1981 brought the first discussion of a workshop on carcinogenicity testing which occurred in 1985. In 1982, the Section agreed to publish proceedings from selected meetings. In this era, the relationship between industry and FDA statisticians was warmed by a re-organization at the FDA into the Center for Drugs and Biologics (CDER). Prior to this point, proof of efficacy discussions between FDA and industry were difficult, but afterwards, they became more collaborative. As a result, there was more participation by regulatory statisticians with the Biopharmaceutical Section membership and professional activities. The Section accomplished another milestone in 1983, when a Manual of Operations was created to help the BPSS officers who were flowing through the organization.

The mid-1980s brought a new initiative of focused research for the Section. Although the informal committees of the 1970s focused on two specific issues, there were no formally established subgroups contributing to the academic problems that the Section faced. In 1983, a Future Goals Committee was created by the Biopharmaceutical Executive Committee and began work in earnest. This was a committee under the umbrella of the ASA Biopharmaceutical Section Work Groups, both chaired by Karl Peace. In 1984, new members were recruited via the *Amstat News* and within 2 months, 70 subsection members had volunteered. Four of these working groups sponsored luncheon discussions at the ASA Annual

Meeting. Karl organized 12 "working groups" that considered special topics related to the pharmaceutical industry. Topics ranged from "Positive Control or Active Control Equivalence Studies" to "Pooling of Data", and from "Analysis of Trials with Incomplete Data" to "Dual Control Groups in Rodent Carcinogenicity Studies". The collective efforts of the work groups were published by Marcel Dekker, Inc., in 1990, under the title: "Statistical Issues in Drug Research and Development", which was Edited by Karl Peace, with royalites from sales of the book donated to the Biopharmaceutical Section of the ASA[3]. The carcinogenicity workshop was confirmed and another membership survey was planned. Early in 1985, David Gaylor and other government statisticians organized the Section's first symposium on long-term animal carcinogenicity studies in Bethesda, MD, and over 200 people attended this successful meeting. Between the 1984 and 1988 Joint Statistical Meetings, these groups were responsible for 10 sessions (many invited), 29 roundtables, and at least 47 individual presentations at various conferences.

Many developments occurred regarding conferences and meetings during the mid-1980s. Continuing education courses gained much popularity. The published proceedings expanded to include some of the MBSW papers, as well as papers from the Princeton Conference, which represented the portion of the program sponsored by the Biopharmaceutical Section. The Biopharmaceutical Section held a joint meeting with the American Society for Clinical Pharmacology and Therapeutics. It also approved plans to co-sponsor a symposium on carcinogenicity with the International Life Sciences Institute. In 1986, plans for participating in the 1989 ASA Sesquicentennial were approved. Initial planning began towards a special issue of Journal of the American Statistical Association (JASA) on biopharmaceutical topics. The first short course was sponsored in 1986: Fundamentals of Clinical Trials. The speakers were Dave DeMets and Gordan Lan.

Support for planning and organizing the vast technical programs of the section became evident in the late 1980s. Early in 1987, the Biopharmaceutical Section officers recognized this need, and a new set of officers was proposed. The 3-year series of positions for Program Chair-elect, Program Chair, and Section Fellow Committee were created. A summary of Biopharm Section members who were elected ASA fellows through 1988 can be found in Appendix H.

A number of special events at meetings and conferences marked the late 1980s. In 1987, the very busy and well-attended ASA annual meeting was highlighted by the presentation of a special plaque to Fred Leone. The Section honored Fred's contributions to the ASA and especially his role in the formation and growth of the Biopharmaceutical Section. The presentation ceremony included individual expressions of appreciation from several members, including Bob Assenzo, Mike Free, Marti Hearron, and Charlie Sampson.

In 1988, the Biopharmaceutical Section was one of three that sponsored the Mid-winter Meeting in San Antonio. The animal carcinogenicity symposium was quite successful from a content and financial perspective, and served to seed future initiatives. The Section sponsored four continuing education tutorials at the ASA Annual meeting. At the business meeting, the members heard that several of the working groups had accomplished enough to develop manuscripts, and plans for a bound publication were in process.

Acknowledgements

A number of individuals have provided valuable perspective and insight into this document. Without their input, the authors would not have been able to piece together as complete of a history as we have. Appendix A contains notes that were instrumental in an effort to document the Biopharmaceutical Section History. These notes were prepared by S. Michael Free and delivered orally in an invited session at the American Statistical Association's Sesquicentennial meeting in 1989, Washington, DC. As current members of the section, we are grateful for their input in compiling the heritage of this organization.

ASA
Monica Clark
Patsy J. McClellan
Megan Murphy
Steve Porzio
Elaine Powell
Carole Sutton

Academia
Fred Leone
Karl Peace

Industry
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Joe Ciminera
Joe Meyer
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Marie-Jan Short – editorial support, Eli Lilly & Company

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2004 FDA/Industry Workshop

Ken Koury

From every perspective, the 2004 FDA/Industry Workshop was an enormous success. Held at the newly renovated Marriott Wardman Park in a historic Washington, DC setting, the location was ideal, the program was exciting, and registration for this popular series of workshops set an all-time record of 518. Even the weather cooperated this year!

All four short courses (Tuesday, September 21) were well received, and all were sold out. Dave Christiansen, Christiansen Consulting, and Steve Wilson, CDER/FDA, presented *Communicating with FDA Statistical Reviewers: Developing Guidance Describing Documentation of Analyses and Analysis Datasets*. This course described the guidelines being developed by FDA statistical reviewers on standard documentation of analyses with particular attention to the clinical trial datasets and associated programs that are submitted to the FDA. In a parallel morning session, Danyu Lin, University of North Carolina, described the *Analysis of Multivariate Failure Time Data* using various statistical models that featured non- and semi-parametric inferences based on relevant marginal distributions. Two parallel short courses were also held in the afternoon. Brad Carlin, University of Minnesota, presented *Bayesian Approaches for Clinical Trial Design and Analysis*, emphasizing the value of these methods to statisticians and regulators involved in drug development. Advantages include the ability to combine information from separate but related sources, reduce sample size, and directly measure the effects of interest while protecting overall error rates. In the other session, *Multiple Imputation for Missing Data in Clinical Trials*, Rod Little, University of Michigan, discussed improved methods for handling missing data, focusing on a maximum likelihood (ML) approach, as well as on multiple imputation (MI).

Four general sessions were held on Wednesday, September 22, and all were rated highly by workshop attendees. The opening session featured Janet Woodcock, FDA, who described the Agency's "Critical Path Initiative" and gave her thought-provoking perspectives on the state of drug development, as well as challenges for the industry and regulators. Robert O'Neill, FDA, described the statistician's increasing role in evaluating the safety of new drug products. In the second session, Don Berry, MD Anderson, Gordon Lan, Aventis, and Susan Ellenberg, FDA, discussed the rationale, controversies and approaches to using flexible trial designs, and attendees were particularly interested in the successes achieved by implementing adaptive randomization procedures in clinical trials of oncology products. Attendees reported that the session on non-inferiority trials was very useful and relevant to their work, based on the thorough discussion of this topic provided by Sue-Jane Wang, FDA, Gary Koch, UNC, and BrianWiens, Amgen. The topic of the final general session was quantifying the relationship between risk and benefit, presented by Tom Permutt, FDA, Reed Johnson, RTI, and Dave Bristol. As more statisticians are becoming involved in risk assessment, this session was considered informative and useful, with an interesting economic perspective.

Nine parallel sessions (three sessions in each of three time slots) were held on the final day of the Workshop, Thursday, September 23. Although certain sessions drew a larger audience than others, all of the parallel sessions were considered as among the most useful of the Workshop by some attendees. This is an indication of the appeal and relevance of the overall program which accommodated the diversity in the interests of attendees. In fact, a recurring theme in the Workshop evaluations was that the parallel sessions were useful because they dealt with specific issues or problems, they were directly applicable to the workplace, and because many of the presentations were excellent. The non-inferiority (general session) and gate-keeping sessions were highlighted on many of the evaluation forms, and comprehensive reviews of these popular topics, prepared by Gary Koch, UNC, are still available on the ASA website for workshop attendees. Other highlights included the sessions on missing data and surrogate markers, as well as excellent sessions on data standards, statistical tools for accelerating drug development, and advisory committees/regulatory review.

The roundtable luncheons were a new addition for the 2004 Workshop, and the response by attendees was extremely positive. Look for these to continue in 2005. The "birds of a feather" sessions at the end of the final day were another feature that brought smaller groups of statisticians with similar, more focused interests together. Topics included statistical issues in orphan diseases, clinical/nonclinical statistical synergy, and dynamic randomization.

The Workshop co-chairs, Steve Wilson from the FDA-CDER and Ji Zhang from Sanofi-Synthelabo Research, deserve a special thank you for leading the organizing committee in developing an interesting, informative, and useful program and selecting an excellent set of speakers. Kathleen Wert, from ASA, did an outstanding job of planning the Workshop and ensuring that all of the details that were so important to its success were taken care of in an efficient and pleasant manner. Planning for the 2005 Workshop is underway, and fortunately for the Section, Kathleen will continue as a key member of the team. The final location and dates for the 2005 Workshop have not been selected yet, but it will be held in September in the Washington, DC metropolitan area. Stay tuned for more details! ■

Minutes of the ASA Biopharm Executive Committee Meeting at JSM 2004 at Toronto, Canada

10 August 2004 (Abridged Version)

Amit Bhattacharyya

1. Introduction and Welcome

Keith Soper

Attendees: Demissie Alemayehu, Keaven Anderson, Amit Bhattacharyya, Christie Clark, Steve Gulyas, Mani Lakshminarayanan, Kay Larholt, Stacy Lindborg, Margaret Minkwitz, Katherine Monti, Kannan Natarajan, Anna Nevius, Len Oppenheimer, Aparna Raychaudhuri, Wasima Rida, Nancy Smith, Keith Soper, Neil Thomas, Naitee Ting, Brian Wiens, Jim Whitmore, Ji Zhang.

2. Approval of Minutes

Amit Bhattacharyya

The latest version of the minutes has been accepted.

3. Corporate Sponsors

Len Oppenheimer

- $18,250 from 19 sponsors was raised in 2003. Preliminary estimates show that $24,000 was raised from 27 new companies (plus one carryover, Lilly) in 2004 so that currently there are a total of 28 Corporate Sponsors (about a 50% increase from 2003).
- All but one of the 2003 sponsors are repeat donors with 9 new additions, including more CROs, software companies and smaller biotech companies.
- Brian Wiens will be the new chair of the committee. Jim Collaianne will join the committee. Kay Larholt and Russ Helms will continue as members of the committee.
- Future work for this committee includes (a) tracking contributions from company decision-makers to the ASA Office (Carolyn Kesner) to Biopharm Section account to Corporate Sponsor Chair; and (b) continuous improvement on all the processes.
- Plans for 2005 are to maintain or increase numbers slightly (i.e., # of contributors and total amount contributed).

4. Budget Update

Kalyan Ghosh

Kalyan was not present at the meeting. Budget is within control, and there is no issue.

5. ENAR and JSM 2004 Report

Luncheon Roundtables

Kannan Natarajan

In future, Biopharm sponsored luncheon roundtable chairpersons will be requested to write a brief report on the discussions at their tables.

Invited and Contributed Sessions

Anna Nevius

Suggestions were made that the presentation slides from the Biopharm sponsored invited sessions be available at the website.

- Permissions from presenters needed before placing these in the Biopharm websites. If agreed, this will be applicable from 2005.

Short Courses

Anna Nevius

- 3 short courses (2 co-sponsored with Bayesian section).
- Attendance around low-40's in 2 of the courses.

6. Best Contributed Presentation Award

Christie Clark

- A student from Carnegie Mellon has been awarded the best presenter. An honorable mention was made to another presenter as well.
- Getting volunteers for distributing the evaluation form has always been a problem. The chairs (of the sessions) have responsibility to get volunteers to distribute and collect the evaluation. Future Program Chairs should send a note to all session chairs noting this responsibility.
- 26 Topic Contributed and Contributed papers and 3 more (jointly with Biometrics) have been included for the competition this year. A proposal was made that only those sessions for which Biopharm is the primary sponsor should be included in the competition.

7. Best Student Paper Awards

Aparna Raychaudhuri

- 2 joint ($1000 each) best student papers awarded, and 3 honorable mentions ($200 each). There were 9 papers submitted. It really helped with the papers coming early. The committee agreed to continue early submission for 2005 as well. The submission guidelines also helped.
- Discussions about the award amount and any recommendation for changes will be discussed at the transition meeting (with budget consideration).
- Suggestion was made to give student paper winners and honorable mentions a seat at a roundtable.

8. FDA / Industry Workshop

Ji Zhang

- 150 hotel rooms booked (until end of last week).
- 300+ to make it break-even. 160 registered so far.
- Honorarium for some speakers needs to be paid. Some travel money needs to be paid for speakers from academia.

9. ENAR and JSM 2005 Report

Luncheon Roundtables

Christie Clark

- Kathy M. interested in organizing a "student" roundtable on a topic related to "Careers in Statistics". A subcommittee can be formed to discuss this further and make a proposal at the Transition meeting. Nancy S., Kay L. and Stacy L. volunteered. Ji Z. and Keith volunteered as well if needed.

Invited and Contributed Sessions

Kannan Natarajan

- 29 competing sessions up for grab (Biopharm has 4 allocations guaranteed and 2 more from competition). 14 Biopharm proposals have been submitted.
- Note that one speaker cannot speak in 2 sessions.

- Post-Meeting Note: The following sessions are selected for the Invited Session at JSM 2005:

1. **Session 200052:** Bayesian Methods in Cancer Research - Sunday, August 7, 2005, 14:00 - 15:50 hrs
2. **Session 200101:** Pharmacogenomics - Monday, August 8, 08:30 - 10:20 hrs
3. **Session 200078:** Importance of "P-values" in Drug approval process - Pros & Cons. - Monday, August 8, 10:30 - 12:20 hrs
4. **Session 200106:** Statistical Issues and Methodologies for the New Biomolecular Technology Age - Tuesday, August 9, 08:30-10:20 hrs
5. **Session 200084:** Assessing information in clinical trials to enable better development decisions. - Tuesday, August 9, 14:00 - 15:50 hrs
6. **Session 200028:** Proof of Concept Strategies - Aspects of Study Design & Analysis. - Wednesday, August 10, 08:30-10:20 hrs
7. **Session 200075:** Dynamic Allocation of Patients in Clinical Trials - Thursday, August 11, 08:30 - 10:20 hrs
8. **Session 200056**: Industry use of SNPs/Haplotypes and Microarrays in Clinical trials - Thursday, August 11, 10:30 - 12:20 hrs

Short Courses

Kannan Natarajan

- Some proposed courses are: "Adaptive Design", "Bayesian Methods", "Data Mining". "Microarray" and "Multiple Comparisons (w.r.t. Safety)" are also mentioned.

10. Publications, Proceedings, and *Biopharm Report*

Kevin Anderson, Jim Whitmore

- Two reports are expected to be issued this year. Next issue is in November. Demissie is looking for topics. A summary of section activities at JSM 2004 will be included.
- There are still issues with the e-mail list. Around 5% addresses are still incorrect. Some of the e-mails are screened out by spam-blocking filter. Some people still want a paper copy.
- Council of Sections reps reported that Monica Clark is setting up a process for keeping current distribution lists for all sections. **ACTION Neal T : to follow-up with Monica for status. ACTION UPDATE: Done. Distribution lists can be used from Nov 2004.**
- Question: If someone writes an article in *Biopharm Report*, can he/she publish this as a paper in a journal? Is there a copyright issue in this? **Action Keith S.: Formally check this with ASA (Bill Smith). ACTION UPDATE: Done. It is not an issue.**

11. Pharmaceutical Statistics Journal Proposal

Jim Whitmore

- Jim got the "Task Force Report" in an e-mail. Biopharm did not get a chance to respond or agree with; we should make some comment to this point.

12. Membership Committee

Avital Cnaan

- Updates were provided from the Council of Section Meetings.

1. Feedback was requested from the section regarding restructuring JSM.
2. ASA plans to have Invited Session based on (i) "attendance"; and (ii) number of papers submitted by the sessions.
3. Sections will be contacted to provide input into the brochure for advertisement. The committee believes that the Membership Committee can represent the section in this regard.
4. Allocation of "Invited Session" to Special Interest group: The committee feels that these groups should not be given an "Invited Session" automatically. They can either be in the competitive pool for the Invited Sessions or do

"Topic Contributed" sessions or partner with other sections for an "Invited Session".

- Few suggestions were made by the committee as feedback; (a) Stratifying sessions by topics is useful; (b) Best Poster Award will be nice; (iii) Cost of Poster vs Rooms need to be evaluated; (iv) Proceedings cost be added to the registration; (v) The Abstracts can be published into a CD-Rom instead of a thick brochure.
- One of the challenges for the membership committee is how to keep the new members active? Can a Joint Section Membership be offered as a compromise? These should be discussed in the future.

13. Nominations Committee

Nancy Smith

- Anyone interested or with suggestions should contact Nancy S. for Nominations (for Chair, Program Chair, Council of Sections) by Oct.

14. Liaison Reports

Midwest Biopharm Workshop

Stacy Lindborg

Deming Workshop

Nandita Biswas

- The 2004 conference will be held in Tropicana, Atlantic City, NJ from December 6 through 10. The website ***http://www.demingconference.com/ contains the program.***

15. Section History

Stacy Lindborg

- Charlie Sampson, Bob Davis, Marti Hearron, Stacy Lindborg, and Steve Gulyas have been meeting bi-weekly to advance this document. The scope will be Biopharm Section History (1966-1988). The goal is to have a draft document ready for distribution by the transition meeting in November. Once published, the committee will need direction for where to publish this document (*Biopharm Report*?) as well as who (both lawyers and other section representatives) should review. Post-Meeting Note: Mike Conlon (Univ. of FL) will be reviewing this document from a legal perspective.

18. Transition Meeting Schedule

Keith Soper

- The Transition Meeting will be on the 12th November at the ASA Office in Alexandria, VA.

Editors' Note: *A link to the full meeting minutes may be found on the Biopharmaceutical Section website.* ■

Corporate Sponsorship Program

Brian Wiens
Chair, Corporate Sponsors Committee

As a section, we are deeply indebted to our corporate sponsors who provide support for ongoing activities. In 2004, we have 28 corporate sponsors.

We are also indebted to Len Oppenheimer, who accepted the challenge of starting the Corporate Sponsors program in 2002. Current members of the Corporate Sponsors Committee include Russ Helms of Rho, Inc., Kay Larholt of Boston Scientific Corporation and Jim Colaianne of R.W. Johnson Pharmaceutical Research Institute. Without their assistance, this committee would not be viable.

The Biopharmaceutical Section is the largest and one of the most active sections in the ASA. With help of our corporate sponsors we are able to provide unique benefits to our members. We are able to sponsor and co-sponsor several meetings throughout the year, including the FDA-Industry Workshop, the Midwest Biopharmaceutical Statistics Workshop and the Deming Conference. We are able to award cash prizes to the Student Paper Awards and the Best Contributed Paper from sessions sponsored by the section at the Joint Statistical Meetings.

Invitations to become corporate sponsors for 2005 were mailed in January. Any company desiring to become a corporate sponsor can also contact the chair of the Biopharmaceutical Section, Len Oppenheimer (*Leonard_Oppenheimer@Eisai.com*) or the chair of the Corporate Sponsors Committee, Brian Wiens (*BWiens@Amgen.com*). ■

2004 Biopharmaceutical Section Corporate Sponsors

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Let's Hear from You!

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