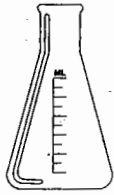


Biopharmaceutical Section



American Statistical Association

Biopharmaceutical Report

Volume 4, No. 1

Winter 1996

Chair: Gary L. Neidert

Co-Editors: Curtis Wiltse and Bill Huster

Letter from the Chair

Gary L. Neidert

Pharmacia and Upjohn, Inc.

It is a pleasure to serve you as the Section Chair for the coming year. The Section continues to grow. We currently have over 1500 members and are the third largest section in ASA. Our list of supporting activities has expanded to match this growth. With this first communication, I would like to give you an update on who will be involved with Section operations and the major activities that are planned for the year.

Section Operations

The Section Executive Committee that will be serving you for 1996 consists of fifteen people; the two Section Representatives serve as ex officio members. The nine individuals who are serving due to election are: Lilliam Kingsbury (Immediate Past Chair), Gary Neidert (Chair), Bob Davis (Chair Elect), Jeff Meeker (Secretary-Treasurer), Steve Snappin (Program Chair), Liannng Yuh (Program Chair Elect), Janet Begun (Publications Officer) and Denise Roe and Sally Greenburg (Council of Sections Representatives). The remaining six committee members are appointed. Each year the new chair appoints two individuals to serve a 3-year term. Previous

see SECTION, page 2

Biostatistics and the Internet: The World Wide Web (WWW)

Sally Greenberg

Berlex Laboratories

This past year has given rise to a tremendous increase in the number of Biopharmaceutical statisticians gaining access to the Internet. Along with that, however, there has been a huge growth in the number of interesting resources, sometimes making it an ominous task for the new user to find out what is available. This article will highlight many of these resources, attempting to give a starting point to both new and experienced Internet users.

There are several types of relevant resources and tools, collectively referred to as "The Internet"; mailing lists, news groups (USENET), the WWW (World Wide Web), FTP (File Transfer Protocol), TELNET, and GOPHER are the more common ones. This article will address the World Wide Web.

The World Wide Web (WWW), also known as "The Web", has taken off at an amazingly fast pace over the last year. Web browsers (the software used to access the Web) have become both amazingly sophisticated in what they can do and simple to use. The most popular browsers are Netscape (Windows, Macintosh, and

see INTERNET, page 2

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appointees who continue to serve are Charles Davis (third year), Wayne Weng (third year), and Shein-Chung Chow (second year). Our new appointees are Phil Pichotta (replacement), Spencer Hudson, and Christy Chuang-Stein.

There are four appointments that serve on the Section Advisory Board who help the Executive Committee perform Section business. These include Bill Huster and Curtis Wiltse (*Biopharmaceutical Report* editors) and Bob Rathmacher (Midwest Biopharmaceutical Statistics Workshop Liaison). Appointments still need to be made for the Work Group Coordinator and the ASQC Conference on Applied Statistics Liaison.

We currently have three committees that the Section needs to keep active: Membership, Finance, and Continuing Education. Each committee's charter is detailed in the Section's Manual of Operations. We hope to change that situation. The appointed committee chairs for this year are Christy Chuang-Stein (Continuing Education), Spencer Hudson (Finance) and Phil Pichotta (Membership). All three committees have a slate of planned activities and need additional members appointed. If you are interested in serving and would like more information, please contact the committee chair.

Section Activities

Our Section will be sponsoring four invited paper sessions this year. Tom Dobins has organized a session on Equivalence Trials at ENAR. Three sessions will be sponsored at the Annual Joint Meetings. The titles and sponsor of those sessions are: Statistical Analysis of Combination Drugs/Chemicals (Sarat Sarkar), Greater Efficiency in Clinical Trials while Preserving Statistical Validity (Jay Herson), and Methods for Analyzing

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Recurrent Events (Katherine Lipschultz). Papers presented at Section-sponsored sessions will be evaluated; awards will be given to the best paper presented and the best by a student.

We will also be coordinating and presenting 8 - 10 Luncheon Round tables at the Joint Meetings. Recruitment of topics for discussion and their final determination will be directed by the Work Group Coordinator.

We will try to have at least two publications of the *Biopharmaceutical Report* this year. One issue will present the second paper produced by the Population Modeling Work Group.

Potential Section Activities

Money has been allocated to enable the Membership Committee to survey the Section. The purposes of the survey are to generate descriptive statistics on the profile of our membership and to determine the services expected by Section members.

Money has also been allocated so that the Continuing Education Committee can begin planning the presentation of a workshop on the collection and reporting of adverse events. This workshop will differ from past ones in that a major deliverable will be to produce a Section "position paper" on this topic.

An attempt will also be made to present again the half-day introductory workshop on the role of the statistician in the pharmaceutical industry, which has been so well received in the past.

As you can see, there is much work to be done. I speak for the entire Executive Committee in stating that we look forward to serving you this year. Elsewhere in this publication is a list of our telephone and fax numbers. Please do not hesitate to contact any of us with questions, suggestions, or concerns.

INTERNET, *continued from page 1*

UNIX), Mosaic (Windows, Macintosh, and UNIX), and Lynx (UNIX). Also, several Internet providers have proprietary browsers. Both Netscape and Mosaic are available without charge (via FTP) for individual use.

The Council of Sections of the ASA has recently formed a committee to get a Web site for the ASA and its Sections. The main site (i.e., home page) for ASA is at:

<http://www.amstat.org/>

The ASA site covers a wide range of material. Consequently, it is an excellent place to begin a search for information. In addition to general ASA information and news, it includes a 6 month calendar of events, Section pages, Chapter pages, details of national, regional, and local meetings, schools granting degrees in statistics, and links to other Statistical Societies, electronic resources, and granting agencies.

Several Sections of ASA (Section on Bayesian Statistical Science, Section on Quality and Productivity, Section on Statistical Consulting, and Section on Statistical Graphics) now have sites up and running. All of these are accessible from the ASA home page. A first draft of the Biopharmaceutical Section home page should be available, as well, by the time this issue of Biopharmaceutical Report goes to press.

A few other statistical organizations also have Web sites. In addition, there are many, many other useful sites available. At the end of this article is a list that I've compiled (building on the work of too many others to credit) of some relevant sites. These sites cover a tremendous range of materials. There are sites whose sole purpose is to index other sites. There are

electronic journals and electronic versions of documents available in print. There are government agency sites. There are sites containing statistical programs. There are sites containing statistical mailing list information. There are pages where you can look up e-mail addresses of colleagues. In addition, there are many sites which are temporary in that they contain information which will quickly become outdated, e.g., conference schedules and abstracts; because of their temporary nature, these are not included in the list at the end of this article. The Web has exploded to the extent that compiling a complete list of statistical and biopharmaceutical sites would be a monumental, never-ending task. Fortunately, most sites have links to other relevant sites, so tracking down a specific piece of information is generally straightforward. The sites listed below represent only a small percentage of the amount of information available.

Have fun!

Composite Resources/Good Starting Points:

<http://www.yahoo.com/>

Yahoo (not a statistical site, but a wonderful search engine which frequently will find the site you're looking for)

<http://lib.stat.cmu.edu/>
StatLib

<http://www.stat.ufl.edu/>
University of Florida Statistics Virtual Library

<http://www.indiana.edu/~statmath/network.html>
Stat/Math Resources on the World Wide Web

<http://www.isds.duke.edu/stats-sites.html>
Statistics Servers & Many Other Links (including links to

- Statistical Departments around the World)
<http://www.biostat.washington.edu/Xvlib/>
 Univ. of Washington Biostatistics Virtual Library
<http://www.biostat.washington.edu/~arossini/stat-services/>
 Guide to Biostatistics Information Sources
<http://asa.ugl.lib.umich.edu/chdocs/statistics/general.html>
 Guide to General Statistical Resources
<http://fourier.dur.ac.uk:8000/stats/other.html>
 Guide to Statistics Resources

Statistical Societies:

- <http://www.stat.sc.edu/~piegorsc/enar.html>
 ENAR
<http://www.stat.unipg.it/iasc.html>
 International Association for Statistical Computing
http://www.mathstat.flinders.edu.au/stats/stat_soc.html
 The Statistical Society of Australia Inc
<http://www.math.ruu.nl/bernoulli/>
 The Bernoulli Society for Mathematical Statistics & Probability
<http://www.mast.queensu.ca/~ssc>
 Statistical Society of Canada

Statistical Mailing Lists:

- <http://www.stats.gla.ac.uk/allstat/introduction.html>
 ALLSTAT
<http://www.AMS.Med.Uni-Goettingen.DE/~rhilger/Biometry.html>
 Hilgers' Links to Biometry
http://www.AMS.Med.Uni-Goettingen.DE/~rhilger/ListS_B.html
 ListServer Biometry
<http://www.AMS.Med.Uni-Goettingen.DE/Mail/biometry/>
 ListServer Biometry Archives
<gopher://nisp.ncl.ac.uk/00/lists-k-o/minitab/files/list-of-lists>
 List of Statistics Lists

Statistical Computing:

- <http://www.sas.com/>
 SAS Institute
<ftp://ftp.sas.com/>
 SAS Institute
<gopher://gopher.uga.edu:8999/11/UGA%20Departments/sug>
 SAS User Group Gopher: Univ. of Georgia
<gopher://gopher.vt.edu:10010/02/5/62>
 SAS/GRAPH Version 6 Tutorial & Handbook
<http://www.nsf.gov/>
 National Science Foundation Home Page
<http://www.research.att.com/cgi-wald/dbaccess/32>
 netlib (Mathematical and Statistical Software)
<http://www.spss.com/>
 SPSS
<gopher://gopher.vt.edu:10010/02/5/127>
 Guide to Using SPSS
<http://www.statsci.com/>
 StatSci (S-Plus) Home Page
<http://www.stat.math.ethz.ch/~roosen/S-faq.html>
 Frequently Asked Questions about S and S-Plus

- <http://lib.stat.cmu.edu/s-news/>
 S-news Archive
http://asa.ugl.lib.umich.edu/chdocs/statistics/stat_guide_home.html
 A Guide to Statistical Computing Resources on the Internet
<http://stat.umn.edu/~rcode/xlispstat-resources.html>
 Xlisp-Stat Home Page
<http://www.graphpad.com/www/welcome.html>
 GraphPad Software Home Page
<http://www-prophet.bbn.com/>
 Prophet Software

Electronic Journals/Bulletins:

- <http://wwwmaths.anu.edu.au/ims/>
 Institute of Mathematical Statistics Bulletin
<http://www2.ncsu.edu/ncsu/pams/stat/info/jse/homepage.html>
 Journal of Statistics Education
<http://www.stat.ucla.edu/journals/jss/>
 Journal of Statistical Software
<http://www.emath.fr/ps/psEng.html>
 European Series in Applied and Industrial Mathematics: Probability and Statistics

E-Mail Directories:

- <http://www.mast.queensu.ca/~ssc/members.htm>
 Statistical Society of Canada Electronic Mail Directory
<http://fourier.dur.ac.uk:8000/stats/edas/>
 e-Directory of Academic Statisticians [searches: UK DAS, Allstat, Bayes-news, Stat-1, Edstat-1, & Sci.stat. * posters for any last name you specify!]
<http://www.ictp.trieste.it/Canessa/ENTRIES/entries.html>
 WHO's Online [e-mail addresses & brief biographies by profession, no statisticians yet]
<http://www.stats.gla.ac.uk/directory>
 UK Directory of Academic Statisticians

Government Agencies/Research Centers:

- <http://www.fedworld.gov/>
 FedWorld Information Network
<http://www.cdc.gov/>
 Centers for Disease Control
<http://www.os.dhhs.gov/>
 US Department of Health & Human Services
<http://www.fda.gov/fdahomepage.html>
 FDA
<http://www.nih.gov>
 National Institutes of Health
<http://text.nlm.nih.gov:80/ahcpr/ahcpr.html>
 Agency for Health Policy and Research Guidelines
<http://www.os.dhhs.gov:80/resdata.html>
 Department of Health & Human Services Research & Data
<http://www.ncbi.nlm.nih.gov/>
 National Center for Biotechnology Information
http://www.nlm.nih.gov/top_level.dir/nlm_online_info.html
 National Library of Medicine Online Information Services
http://www.nlm.nih.gov/extramural_research.dir/visible_gallery.html
 National Library of Medicine Images from the Visible Human Project

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<http://www.open.gov.uk/mca/mcahome.htm>

Medicines Control Agency, UK

<http://s700.uminho.pt/ec.html>

European Community Home Page

<http://www.who.ch/>

The World Health Organization

<http://www.fhcrc.org>

Fred Hutchinson Cancer Research Center

<http://www.law.vill.edu/Fed-Agency/fedwebloc.html>

Federal Web Locator (includes access to Code of Federal Regulations)

Other:

http://seamonkey.ed.asu.edu/~behrens/teach/WWW_data.html

B's Wide World of Web Data

<http://seamonkey.ed.asu.edu/~behrens/>

Research Methods Resources from College of Education
Arizona State University

<http://www.exit109.com/~zaweb/pjp>

Health Economics, Medicine and Pharmacy

<http://cns.bio.com/bio.html>

BIO-Online (Biotechnology information)

[If you'd like to be a part of the development process of the Biopharmaceutical Section Home Page and links, please e-mail Sally Greenberg: Sally_Greenberg@Berlex.com]

Section News

Workshop on Adverse Events

Christy Chuang-Stein,
Chair, Continuing Education Committee

The Continuing Education Committee of the Biopharmaceutical Section of the American Statistical Association plans to sponsor a workshop on adverse events. The workshop is designed to address issues such as the collection of symptoms vs. syndromes, window of event collection after study treatment discontinuation, collection of adverse events at baseline, definition of expected/labeled vs. unexpected/unlabeled, analysis of adverse event data, and presentation of adverse events for drug labeling, etc. In addition, the workshop will serve as a forum where the standard operating procedures for recording adverse events in selected pharmaceutical companies will be presented and discussed.

This workshop differs from many other ASA-sponsored workshops in that it deals with a non-technical subject. However, considering the amount of effort that we spend in collecting adverse event data in clinical trials, the Committee

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feels it is important that this topic receives more attention than it currently does. In addition, the Committee hopes to form a Working Group on this subject, with a position paper to be issued by the Group later.

The Committee would like to hear your opinion on this workshop. If you have any suggestions on what should be included in the workshop, please write to Christy Chuang-Stein (see address elsewhere in this issue). If you have other suggestions on how the Continuing Education Committee can serve the Section members, please also let Christy know. The primary charge of the Committee is to serve the continuing education needs of the Section members. The Committee can accomplish its charge only if it hears from the Section members, i.e., you. So, please help.

Relaxed Deadline for Student Paper Competition

Steven Snapinn

Merck Research Laboratories

Students interested in competing for a Student Paper award must be an ASA member and must be the sole author of an abstract submitted to the ASA by the February 1 deadline, with the Biopharmaceutical Section selected. In addition, the student must submit the abstract, a manuscript, and endorsements from the student's advisor and department head to the Section Program Chair. The deadline for these additional items has now been extended from February 1 (as reported in *Amstat News*) to May 1. Please send these items to:

Dr. Steven Snapinn
Senior Investigator
Merck Research Laboratories, BL 3-2
West Point, PA 19486

Best Paper Awards for 1995

C. S. Wayne Weng

Schering Laboratories

Finally, we have the results of the Best Presenters Award at the Biopharmaceutical Contributed Paper Section of the 1994 Joint Statistical Meetings. The three winners are:

First place — L. Gould & J. Heyse, "Simple Methods for Managing Multiplicity";

Second place — F. Whaley, J. Schoenfelder, & C. Pinsky, "Comparing a Standard Diagnostic Procedure to a Second Procedure Used in Combination with the Standard Procedure";

Third place — D. Rom & E. Hwang, "Testing the Equality of Treatment Effects by their Proportion of Similar Responses".

A check of \$500 will be awarded to the first place presenter and a check of \$250 each will be awarded to the second and third presenters during the 1996 ASA meeting.

The Best Presenters Award was established to enhance the quality of paper presentations in the Biopharmaceutical Contributed Paper Section of the annual ASA Conference. The evaluation consists of 6 categories: Contribution, Organization, Verbal Delivery, Visuals, Handouts, and Overall. We encourage all future paper presenters of the Biopharmaceutical Contributed Paper Section to pursue this award.

Minutes of ASA Biopharmaceutical Section Executive Committee Meeting

August 14, 1995, Orlando, Florida

Attendees:

Janet Begun	Spencer Hudson	Steve Ruberg
Shein-Chung Chow	Lilliam Kingsbury	Steve Snapinn
Bob Davis	Ken Koury	Bob Starbuck
Gary Neidert	Wayne Weng	Richard Foley
Harji Patel	Liannng Yuh	Sally Greenberg
Phil Pichotta	Jim Efrid (Health Policies Section)	

Lilliam Kingsbury welcomed the new members of the Executive Committee: Phil Pichotta who will be responsible for membership and Spencer Hudson for finance. She also announced the newly elected officers:

Chair-Elect	Bob Davis, Astra Merck
Program Chair-Elect	Liannng Yuh, Pfizer
Secretary Treasurer	Jeff Meeker, Bristol-Myers Squibb
Council of Sections Representative	Sally Greenberg, Syntex Research

Approval of Minutes

Minutes of the Executive Committee meeting held March 28, 1995 in Birmingham, Alabama were approved.

Midwest Biopharmaceutical Workshop

Bob Rathmacher of Eli Lilly will be the contact for the 1996 meeting.

Work Group Coordinator

Assignment: Lilliam Kingsbury will appoint a new work group coordinator to replace Liannng Yuh.

Sessions at 1996 Meetings

Steve Snapinn reported that the Section has been allocated two invited paper sessions for the ENAR meeting and three for the ASA meeting. In addition, there will be a competition for a possible fourth session at ASA. The following sessions are in the planning stages:

<u>Organizer</u>	<u>Meeting</u>	<u>Topic</u>
To be determined	ENAR	Equivalence Trials
Sanat Sarkar	ENAR	Combination Drugs
Jay Herson	ASA	Sample Size Re-Estimation
Kathy Lipschutz	ASA	Recurrent Endpoints
To be determined	ASA	CPMP Guidelines

Other possible topics include computational chemistry, stability analysis and outcomes research. The Section will co-sponsor sessions on recurrent endpoints and on vaccine trials at ENAR. The ASA deadline for completed invited paper sessions is November 10; the ENAR deadline is unclear.

Post Meeting Note: Joel Greenhouse, ENAR Program Chair, says that we only have one approved ENAR invited paper session, not two. The equivalence trial session, which will be organized by Tom Dobbins, will be for ENAR, and the session on combination drug trials will move to ASA. In

addition, Christy Chuang-Stein will organize a session on the analysis of lab data. One or two of the planned invited paper sessions for ASA may have to become special Contributed Paper sessions.

Best Paper Awards

There was some confusion over the 1995 Best Paper awards (papers presented at the 1994 meeting) that were to have been presented in Orlando. Bob Starbuck volunteered to provide data entry support to prepare the data for analysis.

Assignment: Wayne Weng will analyze the data from the 1994 meeting and announce the winners in Amstat News.

For the 1996 awards (papers presented at the 1995 meeting), Wayne sent out evaluation forms to Executive Committee members for distribution at the 12 contributed paper sessions in Orlando. The winners should be determined early in 1996, announced in the Executive Committee meeting in March and presented at the joint meetings.

Assignment: Shein-Chung Chow will be responsible for the best paper award for 1996, including data entry.

Assignment: Wayne Weng will provide a list of action steps for the whole process of selecting the Best Papers.

Student Award

The committee allocated \$100 for postage to send letters to various statistics departments announcing the competition for best student paper.

Assignment: Chuck Davis will send the competition announcement letters.

The one student award for 1995 will be presented at the business meeting by Denise Roe to Charlie Zhang of UCLA whose paper was "Multivariate Repeated Measurements with a Family of Covariance Structures."

Assignment: Chuck Davis will send an announcement of the 1995 Student Award to *Chance Magazine* and *Amstat News*.

Continuing Education

The Section has no person responsible for continuing education since the program chair has covered this in the past. It would be more efficient to have a separate chair to address continuing education needs of section.

Assignment: Gary Neidert will nominate a CE chair for Executive Committee approval at the November meeting.

Atlantic City Conference

There was no report on the Atlantic City Conference.

Council of Sections

Harji Patel noted that the Section's contribution to the electronic communications project was acknowledged at the Council.

Candidates for Section Officers

Bob Starbuck distributed a list of possible nominees for Section officers.

Assignment: Executive Committee members will send any additional nominees to Bob Starbuck and will rank candidates by 11/3/95.

Treasurer's Report

Bob Davis reported that the Section had \$80,428.36 cash-on-hand as of June 30, 1995.

Budget

The Section's cash level is so high that it jeopardizes ASA's non-profit status. The Section needs to reduce the cash to about two year's operating expenses, currently running about \$20,000 annually. The committee reviewed proposals for reducing cash levels but only those perceived to benefit the Section's membership as a whole were discussed extensively. The committee agreed to:

- Lower section dues to \$5.00, with \$1.00 of dues going to ASA.
- Give another \$1000 for the electronic communication project in 1995.
- Give an additional \$500 per year to the electronic communications project, subject to an annual review by the committee, starting in 1996.
- Give a \$500 one-time expenditure to support the Deming lecture.
- Give a \$500 award to the undergraduate data analysis competition.

Several other ideas will be explored and reported on at the November meeting.

Assignment: Janet Begun will investigate whether the Section should pursue producing a brochure or video on "A Day in the Life of a Biostatistician."

Assignment: Spencer Hudson will determine the cost of providing taped continuing education courses to members.

Assignment: Gary Neidert will ask the Continuing Education Committee to review the feasibility of subsidizing specific topic workshops, such as Russ Wolfinger's Mixed Models workshop.

Assignment: Bob Davis will investigate options on discounting Proceedings charges for members.

Since implementation of these proposals will not reduce the Section's cash to \$40,000 by the end-of-1995 target, the Section must provide ASA with a plan outlining how the Section will reach the target.

Assignment: Bob Davis and Lilliam Kingsbury will submit the financial plan to ASA.

Health Policy Section Workshop

Jim Eford requested Biopharmaceutical Section support for a workshop sponsored by the Section on Health Policy to be held in Boston, December 2-3. The committee agreed to support the meeting with \$800, enough to cover mailing the meeting brochures to Section members. Biopharmaceutical Section members should receive a reduced registration fee for this meeting.

Charter

Gary Neidert noted that by law the entire membership needs to approve changes to the charter. Since several minor revisions have been proposed, we will delay action on them until additional noteworthy changes are identified.

Pharma Activities

The Executive Committee had wondered if there was a need for the Section to assume more of the training responsibility for PMA statisticians. Lilliam noted that PERI, an arm of the new PhARMA, is picking up training responsibilities for the pharmaceutical industry.

Steve Ruberg suggested that the PhARMA lifetime service award be presented at the ASA meeting.

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Assignment: Steve will assess the cost of presenting the award through the Section and will send a formal proposal to Lilliam.

Next Meeting

The next meeting of the Executive Committee will be held at Bio-Pharm Clinical Services, Blue Bell, PA on November 3.

Minutes of ASA Biopharmaceutical Section Executive Committee Meeting

November 3, 1995, Blue Bell,
Pennsylvania

Attendees:

Norman Bohidar	Lilliam Kingsbury	Steve Snapinn
Shein-Chung Chow	Jeff Meeker	Bob Starbuck
Bob Davis	Gary Neidert	Liangng Yuh
Spencer Hudson	Phil Pichotta	Curtis Wiltse

Lilliam Kingsbury welcomed the members of the Executive Committee.

Round Tables

At the 1996 Joint Statistical Meetings the Section will be responsible for 8-10 round tables. There was a discussion of potential people to organize the round tables. There was also a discussion of the balance between clinical and non-clinical topics.

Assignment: Lilliam Kingsbury will appoint by the end of November someone to organize the round tables.

1996 Workshop

Potential topics for a workshop sponsored by the Section and completely independent of any other ASA meetings were discussed. It was decided to hold a workshop during 1996 on adverse event collection and reporting. It is hoped the workshop will lead to a working group on the topic to develop a position paper. It was also determined the workshop would be the responsibility of the Section Continuing Education Committee. There will be a reduced registration fee for Section members.

Work Groups

Liangng Yuh reported that the Population Modeling work group is preparing a second paper for publication. The first paper was published in *Biometrics* (Yuh, et. al., 1994. Population Pharmacokinetic/Pharmacodynamic Methodology and Applications: A Bibliography. pp. 566-575). This is currently the only work group that is active. He requested that a replacement be appointed to coordinate these work groups.

Executive Committee Membership

Gary Neidert appointed Spencer Hudson, Phil Pichotta, and Christy Chuang-Stein to the Executive Committee for three-year terms. Spencer is the Finance Committee Chair, Phil is the Membership Committee Chair, and Christy is the Continuing Education Committee Chair.

Nominating Committee

A slate of candidates for 1996 Biopharmaceutical Section elected offices was presented. The officers to be elected are Chair-Elect, Program Chair-Elect, and one Council of Sections Representative.

Role of Committees

The Chairs of the three Committees (Finance, Membership, Continuing Education) were asked to review the written charges for their respective Committee. The two chairs present were comfortable with them, but felt it was premature at the beginning of their terms to make any changes. A formal review of the written charges was deferred until the end of the current terms of the Chairs.

Two other committees were also discussed: the Committee on Establishing Liaisons to Other Organizations and the Committee to Recommend Statisticians to FDA Advisory Committees. As to the latter committee, if there is interest in it by the FDA, the committee will be put on next year's agenda. If there is not, the committee will be disbanded.

Assignment: Gary Neidert will contact FDA Biometrics (Bob O'Neill) to see if there is interest on their part in the recommendations. If so, he will determine what the procedure is for providing input to the FDA.

Awards

Wayne Weng reported that the 1995 Best Paper Awards for papers presented at the 1994 Joint Statistical Meetings were:

- First - Larry Gould and Joe Heyse, *Simple Methods for Managing Multiplicity*
- Second - Fred Whaley, John Schoenfelder, and Carl Pinsky, *Comparing a Standard Diagnostic Procedure to a Second Procedure Used in Combination with the Standard Procedure*
- Third - Dror Rom and Eunhee Hwang, *Testing the Equality of Treatment Effects by the Proportion of Similar Responses*

It was noted that there was no difference in amount awarded between second and third place. Shein-Chung Chow is responsible to determine the 1996 Best Paper award recipients for papers presented at the 1995 Joint Statistical Meetings.

Biopharmaceutical Report

The lead article in the next issue of the *Biopharmaceutical Report* will be an article on adverse events by Bob Northington. Several other potential topics were suggested, including individual bioequivalence, a series of topics in therapeutic areas, multiple endpoints, combined endpoints, and sample size reestimation. There was also a discussion concerning the lag time between joining the Section and being placed on the mailing list to receive the *Biopharmaceutical Report*.

Nominations for ASA Fellow

Bob Starbuck, the outgoing past chair, reported that no names have been submitted for nomination.

Budget

Bob Davis presented a proposed 1996 budget designed to reduce the Section's cash level to about \$40,000. In addition to those proposals approved at the August 14 meeting, the Committee voted to:

- Reduce the price of the *Proceedings of the Biopharmaceutical Section* for 1996 and 1997 so that ASA receives the same income as before the price reduction and the Biopharmaceutical Section does not receive any income.
- Fifteen hundred dollars (\$1,500) was contributed to the ASA committee responsible for transferring film to an electronic medium.
- Five thousand dollars (\$5,000) was allocated to support the Section-sponsored 1996 workshop on adverse events.
- Ten thousand dollars (\$10,000) was approved to conduct a membership census of the Section. An incentive to respond will be provided to each Section member. It was noted that such a questionnaire may have to be reviewed by the ASA Committee on Surveys. The census is to be completed by the end of 1996.

Assignment: Phil Pichotta will prepare a sample questionnaire. The survey will be conducted by the Membership Committee.

- An additional \$10,000 was budgeted for travel expenses for each of 1996 and 1997. In the past, members of the Executive Committee have been charging their travel expenses to their employing organization, even when the travel is only for the Executive Committee business meeting, and not for attendance at ASA or ENAR meetings. The Section feels that travel for only Section business should be reimbursed by the Section, not by the individual's employer.

Also discussed was a videotape on "A Day in the Life of a Biostatistician." This topic was referred to the Continuing Education and Membership Committees, to be considered for 1997.

Assignment: Bob Davis will draft the budget proposal and forward it to Lilliam Kingsbury and Gary Neidert. It will then be submitted to Penny Young at ASA.

Program

Spencer Hudson reported that we have three invited paper sessions at the 1996 Joint Statistical Meetings, one on Monday, one on Wednesday, and one during the first session on Thursday. The topics are:

- Analysis of Combination Drugs
- Greater Efficiency in Clinical Trials while Preserving Statistical Validity
- Analysis of Recurrent Events.

The program is nearly complete. We are entering the competition for a fourth session on the topic Analysis of Laboratory Data.

We have one invited session at ENAR. The topic is to be Equivalence Trials.

Student Award Papers

The Student Award Papers are not needed as early as the abstracts. The deadline for the abstracts (for ASA) is February 1. It was decided the deadline for the full paper would be delayed until May 1.

Next Meeting

The next meeting of the Executive Committee will be held at ENAR in Richmond, Virginia, March 17-20.

Biopharmaceutical Section Roundtable Discussion For Joint Statistical Meetings - Orlando 1995

Lianng Yuh

Pfizer Central Research

Testing Dose-Response Relationship Based on Ordinal Data

Christy Chuang-Stein

The Upjohn Company

The group first discussed how to compare dose groups when response is measured on an ordinal scale. If the emphasis of the treatment is to get as many individuals in the designated outcome categories as possible, then the ordinal scale should be accordingly dichotomized for the comparison to reflect the primary objective of the treatment. If the superiority of one dose group over another is based on the ability of the former to produce a more favorable outcome in general, the ordinal scale should be utilized.

In testing dose-response relationship, the group discussed two major approaches. The first one applies non-model-based significance tests while the second is based on fitting models to the data. The former includes tests based on association measures, tests related to the Jonckheere-Terpstra procedure, order-restricted tests for continuous response adapted for ordinal response, and tests treating the response distributions as survival distributions. The null hypothesis of no differences among the dose groups is tested against the alternative of a stochastic ordering among the dose groups. It was pointed out during the discussion that due to the confirmatory nature of significance tests, the use of significance tests does not allow one to explore the nature of the dose-response relationship. Therefore, significance testing is only relevant when there is prior knowledge regarding the shape of the dose-response relationship.

As for the modeling approach, the discussion concentrated on the proportional odds models where the effects of different doses can take on different forms. One special case is when the treatment effect is a linear function of the dose or the logarithmic dose. The advantage of the modeling approach is that a good-fitting model lends insight about the form of the relationship and allows one to estimate the probabilities of the various response categories.

The majority of the material for discussion was extracted from a review paper currently under preparation by Christy Chuang-Stein and Alan Agresti.

Use of Serum Drug Concentrations in Design or Analysis of Clinical Trials

Gordon W. Pledger

R. W. Johnson Pharmaceutical Research Institute

Participants in this Roundtable discussion were primarily from the pharmaceutical industry and from academic

medical research centers. The experience of the group covered a wide range of therapeutic areas, with areas of particular interest including cancer research and compliance-adjusted analysis of clinical trials.

The discussion leader's preface to the discussion is summarized as follows: Randomized clinical trial designs often include periodic measurement of plasma drug concentrations. Typically, the trial protocol indicates that the blood samples should be obtained shortly before a dose, i.e., trough concentrations are desired. In actuality, however, many of the concentrations obtained are not trough concentrations, and in other cases the blood sampling time relative to dosing times is unknown. Typically the planned use of these data is vaguely stated in the trial protocol, e.g., "to explore relationships between drug concentrations and response variables" or "to assess compliance." Experience has often shown these plasma drug concentrations to be of limited value. In some cases the plasma samples are frozen and stored but never assayed, presumably because no useful purpose for the concentrations has been identified.

Given this rather disappointing experience, when should drug concentration data be collected, and what should be the goals and uses of these data? To address these goals do we need (or when do we need) different designs, e.g., concentration-controlled designs?

Roundtable participants discussed possible uses of "casual" plasma drug concentrations, i.e., concentrations that are observed under rather loose sampling schedules and are not controlled or used in trial conduct. Possible uses include the following: (i) exploratory analyses examining possible relationships between concentrations and safety or efficacy variables; (ii) compliance information, e.g., demonstration that active drug-treated subjects have detectable concentrations and placebo-treated subjects do not; (iii) information that may help to explain extreme observations, e.g., did a subject with a severe adverse event have an unusually high concentration?

Analysis incorporating these plasma drug concentration data was likened unto analyses taking into account drug compliance in that the appropriate comparison group is usually unclear. There was also discussion of the possible uses, and risks of using, plasma concentrations as a covariate in statistical analyses.

Part of the discussion involved concentration-controlled designs, that is, designs in which treatment groups are randomly allocated to target plasma concentrations rather than to target doses. Experience with concentration-controlled designs has been mixed. Some discussants have found these designs to be very cumbersome and complicated, not worth the trouble. Others have had a more favorable experience. The main areas of concentration-controlled trial experience among the group were cancer and epilepsy. Some of the participants opined that concentration-control led trials should be considered only when the test drug is known to have highly variable pharmacokinetics. Adaptive dose-response designs were mentioned as an alternative approach. There was also discussion of concentration-controlled designs that avoid the burden of continuously measuring plasma drug concentrations on a quick turn-around basis to allow dosage adjustments aimed at more nearly achieving the target concentration. Two antiepileptic drug trials were mentioned as examples; both attempted (by different methods) to obtain an accurate estimate of the appropriate dose for a given subject by using prandomization observations.

Although the discussion did not result in definitive conclusions or recommendations, there appeared to be general agreement as to the following:

1. Clinical trial protocols should explicitly state the planned use of any plasma drug concentrations to be measured. This increased clarity of goals would be expected to lead to better planning of blood sampling schedules and greater attention to compliance with those schedules.
2. The jury is still out with respect to the role of concentration-controlled trials. Where they are thought to be useful, simpler implementations of the concentration-controlled paradigm are needed.

Subset Analysis for Phase II/III Studies

Naitee Ting

Pfizer Central Research

Participants in this roundtable discussion were from the pharmaceutical industry, academia and academic medical research centers. We have discussed a number of issues regarding subpopulation analyses. Our discussion is summarized as follows:

Regulatory Issues

Both sponsors and regulatory agencies tend to pay more attention to the so-called "Confirmatory Trials". These trials usually are Phase II or Phase III Trials, sometimes combined Phase II/III trials.

Sponsors usually are interested in performing subset analyses to exhibit the consistency of the results across various subsets. While investigating the consistency, responders and non-responders may be identified. There are several issues involved in this procedure. The first issue is the appropriateness of running this type of analysis. It was pointed out that according to Yusuf, et al (1991), there are appropriate and inappropriate subgroups. Treatment-dependent subgroups are inappropriate, while subgroups identified from baseline characteristics are appropriate.

The next issue relates to the interpretation of study results if a "responder" subgroup is identified. Suppose there are some baseline characteristics (other than treatment group) strongly associated with the responder subgroup. The sponsor will have to evaluate whether the treatment, or the baseline characteristic, is causing the response. In some cases, treatment can be confounded with baseline factors. Treatment can also be confounded with inappropriate subgroups. Responders are typically identified based on changes of clinical endpoints post baseline. Responder status is not a baseline characteristic, and hence responder subgroup is inappropriate.

If the treatment by subgroup interaction is studied, then we have to determine an alpha level to test for this interaction (0.05, 0.10, or 0.20), and we need also study the consequence of a significant interaction. Interaction tests can provide an early sign as to which covariates should be considered for subset analysis. The lack of a statistically significant interaction should not preclude selection of a covariate from being considered for subset analysis;

Corporate Members

The Biopharmaceutical Section has three types of memberships: regular, student and corporate. The corporate members of the Section, who are also ASA corporate members, provide the Section with \$300 annually in dues. These funds contribute significantly to our annual budget and to our ability to sponsor Section activities.

The current Corporate members of the Biopharmaceutical Section are:

Burroughs Wellcome
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 Sandoz Pharmaceuticals
 The Upjohn Company
 Warner-Lambert/Parke-Davis
 Wyeth-Ayerst Research

The Biopharmaceutical Section gratefully acknowledges its Corporate members and their support.

however, without the interaction test, there is no reasonable approach. Testing the interactions at a high alpha level should provide sufficient protection against missing any "important" covariates.

We also discussed completer analysis vs. intent-to-treat analysis. Completers are again defined by patient responses to treatment, which is an inappropriate subgroup. Intent-to-treat analysis refers to an analysis that includes all of the randomized patients, which is not a subgroup. Such an analysis is helpful in monitoring a study; i.e., if patients dropped out during the monitoring process, the observed data of those patients before they dropped out will be included in the intent-to-treat analysis. Typical intent-to-treat analysis includes not only completers and dropouts, but also patients who were incorrectly enrolled but did not satisfy inclusion/exclusion criteria or who took an unacceptable concomitant medication which was not discovered until completion of the study. Intent-to-treat analyses should contain all of the "dirt" and hopefully show that the validity assignments did not dramatically affect the conclusions of the analysis.

The typical subset analysis is performed in the following order:

- test for a treatment by subset grouping interaction;
- study the response within each subset if the interaction is significant;
- perform further analyses based on findings from above steps;

- design new studies to test for more refined hypothesis.

However, there can be many more ways to perform the subset analysis. It was suggested a multiple regression approach may also be used.

Can we prepare protocols with well-defined subset analysis ahead of time? If so, how to prepare for these analyses in a protocol? We noted that subset analyses are unplanned. Almost all of subset analyses are somewhat "data-driven". Based on study results, statisticians or clinicians may find interesting properties or important questions related to the specific set of results. Exploratory subset analysis is a very useful tool to study these properties or questions. Hence, in general, we can agree that subset analyses are unplanned.

The next natural question would be the p-value adjustment. Should we adjust p-values for unplanned subset analysis? The answer to this question depends on how the subset analysis is used. If the analysis is used in a submission to support a major claim, it is unclear as to whether the p-values should be adjusted or not, and how p-values should be adjusted if an adjustment is needed. Suppose the subset analysis is used to generate a new hypothesis. Then new studies should be designed to test the hypothesis. Based on the results from new studies, the adjustment of p-values in a submission can be a less critical issue. These questions can be more difficult to handle when we are dealing with equivalence trials.

There was a brief discussion about combination of subset analysis. When there is insufficient sample sizes to analyze for a specific subgroup from any single trials, we tend to combine multiple trials to study this specific subgroup. For example, it is a common practice to study female patients, older patients, etc. in a combination of many studies. We did not discuss in depth as to assumptions required in combining these studies, nor did we discuss how inferences could be made from these combinations.

How does subset analysis affect drug labels? Suppose the sponsor performed excessive subset analyses and found certain subgroup(s) provided best patient response to the test drug. This may lead to a restricted drug label such that only the potentially best responders can be prescribed to use this new treatment. It is unclear as to how regulatory agencies view this issue. Suppose that excessive subset analyses may lead to restricted labeling, should we discourage sponsors performing these analyses? However, if there really is a "best subset of responders", such a subset will be identified sooner or later. From a sponsor's point of view, the earlier the subset of responders is found, the better.

There will be a workshop sponsored by FDA in early November. The topic for the workshop is "The new gender guideline". Sarah Kogut (one of the luncheon discussants) is invited to represent the industry statistician's point of view in this workshop. The spirit of this new gender guideline was to encourage sponsors include more female patients/subjects in early clinical trials. This topic created many interesting questions and discussions:

- Why female specific? What about different races/age groups?
- Increase female patients/subjects at which stage? Phase I, II, or III?
- Does the main concern relate to reproductivity? If so, males are subject to the same concern.

- How to evaluate compliance with respect to contraception?
- What are the advantages/disadvantages?
- There can also be confounding problems because some minority subgroups of patients tend to be restricted to a specific community.

There was a discussion about post-marketing issues. In post-marketing studies or epidemiological studies, people are still interested in exploring factors affecting responses. Subset analyses are frequently applied. However, one type of epidemiological study is case control study. In these studies, patients were recruited based on matching disease status. Analysis performed based on predisposing factors identified at design stage may not be viewed as subset analysis.

Scientific Issues

P-value adjustment is not only a regulatory issue, but also a scientific issue. Do we have to consider protecting alpha level in exploratory analyses? What level of statistical significance should be considered in a subset analysis? Is statistical significance more important than clinical significance, or vice versa? We need to clarify the purpose of each subset analysis. If the purpose is to estimate a treatment effect in a certain subgroup, then clinical significance is more relevant. On the other hand, if we are testing for an unplanned hypothesis, then we need to consider the p-value adjustment.

The next question is how to adjust the p-values. Is subset analysis conditioned on the overall analysis? If so, what is the conditional structure? Should we study this problem from a Bayesian point of view? Should we consider Gibb's sampling approach? Should we adjust p-values for multiplicity?

We need to study distributional properties of the whole population. Do we also need to study distributional properties of each sub-population, and each sub-sub-population? Do we have to guarantee normality in each cell? Do we need homogeneous patient sub-populations to maintain statistical cleanliness or we really need heterogeneous subgroups to study each sub-population separately?

Design Issues

Designing a study with subset analysis is very difficult. There was not much experience from discussants at the lunch table in designing studies with subset analysis. We also discussed about protocol preparation and related issues. One major problem is "how to power the study?". Should we power the study based on the combined analysis? Or should we power each subset separately? Which computation will provide a lower sample size estimate? Will such a study lead to restricted labeling? We should discuss with regulatory agencies as early as possible in designing these types of studies.

One other issue that we discussed was about "Lord's Paradox" (Bock, 1975). The example given in the reference was that in analyzing weight gain in students, there was a difference between male and female students. However, the difference disappeared after the data were re-analyzed using baseline body weight as a covariate. The issue here is that in designing studies or in performing subset analysis, we need to consider the covariates that may influence the results. It is important to adjust for these covariates while performing the analysis.

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Strategies for Nominal Alpha level Adjustments for Multiple Endpoints

Walter W. Offen, Ph.D.

Senior Research Scientist
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Jeffrey D. Helterbrand, Ph.D.

Senior Statistician
Eli Lilly and Company

Summary of Discussion:

This roundtable discussion was attended by statisticians with diverse backgrounds, with representation from the pharmaceutical industry, CROs, academia, and medical centers.

The discussion began with the roundtable leader explaining the key point: When each of two variables must show a statistically significant difference, then the nominal levels that should be used must be between 0.05 and 0.2236, inclusive, depending on whether they are perfectly correlated or independent, respectively. This was illustrated later in the discussion by a two-dimensional sketch where the rejection region could be indicated.

The two primary examples that were discussed where one must show multiple endpoints all to be statistically significant were Alzheimer's Disease (AD) and combination trials. In the case of AD, a drug effect must be demonstrated upon a measure of cognition and a clinical global scale. In the case of combination drug trials, one must show that the combination is superior to each of the individual components.

Showing the rejection region in these situations using innovative and creative graphics (pen to paper) led to a spirited discussion of what a reasonable and appropriate rejection region should be. For simplicity, we focused on one-sided alternative hypotheses. Picture a two-dimensional graph with the x- and y-axes corresponding to the variables, with a bivariate normal distribution floating over the top. In the situation where variables 1 and 2 must be significant at the α_1 and α_2 nominal levels, respectively, the rejection region is an infinite rectangular region in the upper right corner of the graph. Ideas such as using curved rejection regions were put forth as viable alternatives. One that may have particular appeal was where the rejection region is defined by drawing a quarter-circle centered at (0,0) with radius $Z\alpha$ connecting the positive sides of the x- and y-axes. At the point where this quarter-circle intersects the x- and y-axes, a line is drawn to infinity overlaying the axes. The algebraic formula for this rejection region would be $(x^2 + y^2) \geq Z\alpha$, with the additional constraints that $x \geq 0$ and $y \geq 0$. $Z\alpha$ would be chosen such that the entire volume under the curve in the rejection region is equal to α . Note that this

rejection region would correspond to the rejection region for Hotelling's T^2 under independence with the additional constraints that $x \geq 0$ and $y \geq 0$.

When computing the Type I error, placement of the null hypothesis needs to be carefully considered. An obvious choice is the origin, (0,0). However, (0, 10σ) is also within the null region. The implication of this is illustrated by the following example. Suppose one has 2 independent variables, normally distributed (so correlation is 0), and furthermore suppose one chooses the rejection region in two-space to be rectangular. One can show that under the null (0,0) that each variable should be tested at the nominal level of .2236 (square root of .05). However, if it is known *a priori* that the study drug has a very large effect upon one of the variables, say variable 2, then a more appropriate null might be (0, 10σ), in which case to maintain an overall Type I error rate of 0.05, one must test variable 1 at the 0.05 level rather than at the 0.2236 level.

The computer program that is being developed by Jeff Helterbrand was discussed briefly. This program computes the overall Type I error and power for any defined rejection region and specification of the null and alternative hypotheses. One can have any number of variables, as well as multiple treatment groups. Further details will be published in the future.

Finally, regarding how to present and interpret the findings with such decision rules, it was suggested to use confidence regions rather than nominal p-values. To illustrate this issue with an example, again consider the case where each of two variables must be statistically significant. Suppose the correlation is small, such that each variable should be tested at the 0.15 nominal level. If the resultant p-values are each 0.12, then by the decision rule we declare the treatment to be effective. Reporting the p-values as 0.12 might confuse nonstatisticians since they did not achieve the typical 0.05 boundary. However, an appropriately constructed 95% confidence region would not contain the origin (0,0), and, hence, this representation of the data would be consistent with the conclusion of effectiveness.

Dose Response For Continuous Response Outcome In Clinical Trials

H. M. James Hung and S. Edward Nevius
Food and Drug Administration

The goals of Phase III dose response trials are often not clear. One possible objective is finding the first study dose that beats the placebo. Some argued that this goal may be just created by imagination and might not be of concern to the medical community. Another objective is identifying the upper end of useful dose range. If the toxicity of the study drug is dose dependent, then the study dose range covering the dose with unacceptable adverse event profile may help to achieve this goal. Some argued that this should be done in Phase II trials. The upper end of useful dose range may be defined as a dose beyond which there is no appreciable increase in drug effect. Some agreed that this goal seems important. It is generally recognized that pairwise comparisons usually done in ANOVA or ANCOVA can not achieve this goal except in some special circumstances, such as planning sample size with the issue of multiple comparisons properly considered and with very high power in detecting

the minimal clinically meaningful difference. In contrast to pairwise comparison, the regression analysis approach using a low-degree polynomial or a simple nonlinear model may offer a better way of describing the dose response profile. For instance, a quadratic polynomial can shed the insight that the drug effect begins to flatten out at some dose in the study dose range. With the regression analysis approach, the general design strategy requires more study doses and fewer subjects per dose, which differs from the design strategy for proving drug efficacy that requires more subjects per dose. Thus, the dose response study should be separate from the dose efficacy study. It might be worth entertaining the thought of doing a dose response study to characterize the dose response that is followed by efficacy study(s) for some target doses. The dose response study may be used as a supportive study for the efficacy of the selected doses.

Issue In Bioequivalence

Shein-Chung Chow

Bristol-Myers Squibb

Individual Bioequivalence

Unlike distributional or population bioequivalence and unlike the criterion for bioequivalence on average bioavailability, individual bioequivalence promotes the concept of "switchability" between formulations to ensure the same safety and efficacy profiles among patients. Currently a decision rule to establish individual bioequivalence does not exist. Furthermore, the definition of individual bioequivalence itself is rather elusive.

The discussion focused on the following two definitions where individual bioequivalence is claimed when the majority of the subjects satisfy the criteria.

- 1) For a given subject, statistically test for bioequivalence of the marginal distributions of the test and reference formulations in terms of the first two moments (i.e.; mean and variance under the assumption of normality). This is a general definition without regard to methodology, however we consider application of a replicated crossover design. This definition may imply population bioequivalence which can imply bioequivalence on average bioavailability.
- 2) For a given subject, bioequivalence is concluded if their relative bioavailability (i.e.; test/reference) is within some predetermined acceptable limits (e.g.; 0.75 and 1.25) as proposed by Anderson and Hauck (1990).

Many statistical methods for the assessment of individual bioequivalence have been proposed (see e.g.; Esinhart and Chinchilli, 1994; Holder and Hsuan, 1993; Schall and Lucas, 1993). However, these methods were not based on definition (1) described above. As a result individual bioequivalence may not imply population bioequivalence or bioequivalence on average bioavailability, which has created some confusion regarding the relative benefits and risks of the individual approach to bioequivalence. We recognized some of the complications involved with safeguarding valid statistical methods such as higher drop-out rates, ethical concerns involved in drawing blood samples, monetary expense, longer trial duration and potential efficiency of precision estimates.

In conclusion, we feel that the concept of individual bioequivalence should be encouraged. We recommend that a decision rule for individual bioequivalence be developed prior to discussions regarding the potential applications.

Alternative Pharmacokinetic Measures

Although C_{max}/AUC has been demonstrated to be a better measure for the rate of drug absorption (Endrenyi, Fritsch and Yan 1991) an example can easily be constructed where two drugs have exactly the same C_{max} and AUC, yet they are not bioequivalent. It is recommended that MRT (mean residence time) be included in addition to C_{max} and AUC for the assessment of bioequivalence.

In Vitro /In Vivo Correlations

The lack of a clarifying position on the relationship between *in vitro* dissolution testing, *in vivo* bioequivalence testing, and therapeutic effect has long plagued the pharmaceutical industry. *In vitro* dissolution may not be predictive of *in vivo* bioequivalence testing which may not be predictive of a therapeutic outcome. As a result a small scale confirmatory clinical trial may be considered since individual bioequivalence methodology may require a larger sample size.

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Book Review

Bolton S 1990: *Pharmaceutical Statistics: Practical and Clinical Applications*, second edition. *Drugs and the Pharmaceutical Sciences*, volume 44. Dekker. 646pp. ISBN 0-8247-8267-4.

Reviewed by Nathan Enas

Statistical and Mathematical Sciences, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA.

There are many introductory statistical texts available today, but if one is studying pharmacy or another health science, Bolton claims that this book is "the only textbook on statistical applications in the pharmaceutical sciences" (at least at the time of its publication). I assume his claim applies only to introductory texts since his book cites several texts dealing with pharmaceutical statistical applications. Although his claim might not be true today, five years since publication, his work certainly is a substantive contribution and worthy of consideration by its intended audience, "pharmacists and health science-related scientists who want to learn statistics". While reviewing this book, I tried to consider the perspective of such a reader.

Even after just a short perusal, it became clear that this book is encyclopedic in nature and probably intent. After the usual introductory material (i.e., definitions, graphics, probability concepts, and sampling) with examples from the pharmaceutical sciences, Bolton covers statistical inference, sample size and power calculation, regression and ANOVA, experimental design, and nonparametric methods. He also has separate chapters for transformations and outliers, quality control, process and assay validation, consumer testing, and optimization techniques. Hence, he discusses practically the entire pharmaceutical development process and the essential statistical methods typically used during the process. Topics particularly noteworthy to this author include power analysis, multiple comparison procedures, various clinical trial designs (e.g., crossover, repeated measures), and consumer acceptance testing.

If encyclopedic breadth is one of this book's strengths, then the correlated lack of depth is a weakness. Most of the more specialized or esoteric topics are covered quickly, and I felt rushed at times while reading them (e.g., Mantel-Haenszel statistics, Winsorizing). Bolton's apparent solution to this is to provide references at the end of each chapter which should be a welcome sight for the reader desiring more information on a certain topic.

Another potential weakness, considering the present level of computerization at schools and businesses, is the absence of any discussion of software that can be of use to the reader. Bolton does recommend the use of such software in his introduction, but his inclusion of "shortcut" formulas shows that he is expecting hand calculations to be performed by at least some of his readership. I believe formulas are useful insofar as they illustrate concepts; however, statistical software is so widely available today that use of and emphasis on formulas should be limited. This practice should decrease "learner's anxiety" among those statistics students who are relatively weak in mathematics and serve to reinforce the important concepts rather than the laborious mechanics of statistics.

The layout of the book is very accommodating to the reader. Bolton makes frequent use of graphics, drawings, and tables to illustrate concepts and applications. Sections are of reasonable length, and examples are used frequently. The exercises at the end of each chapter are interesting and relevant; some are rather challenging (and are labeled as such) and are used by Bolton to "expand the scope of the book". Following the introduction and 16 chapters, there are some useful appendices which cover variance properties, determination of relative potency via tests for linearity and parallelism, and multiple regression.

Some useful statistical tables follow, and the book is concluded with solutions to most of the problems from each chapter and an adequate index.

I found this book (in its second edition) to be a welcome addition to the texts that one can recommend for the pharmaceutical scientist who would like to learn more about both basic and advanced statistical applications. Bolton's diverse experience in this field is obvious, and he shares his experience effectively in this text. If future editions are considered, I would recommend a discussion and use of statistical software throughout the book in place of laborious computations. I would also suggest a discussion of Bayesian probability theory and its many applications in pharmaceutical development to expose the statistical novice to some of the choices available in data-driven decision-making. In all, I believe Bolton has succeeded well at his goal in this book's second edition.

Mission Statement

Biopharmaceutical Section

Because of the particular need for the application of statistics to the development and use of therapeutic drugs and devices in humans and animals, the Biopharmaceutical Section was Formally organized in 1981, previously existing as a subsection since 1966. Primary interests of the Section deal with:

- drug and device discovery and the evaluation of their safety and efficacy
- product development, production, and quality control
- drug toxicity and disease surveillance
- disease prevention and intervention activities

Section Objectives

- To aid the American Statistical Association and its sections in the effort to create, promote, and stimulate interest in the advancement of statistics and its application to the fields of human and animal health.
- To produce publications of research developments and results and other information on topics of interest to health scientists.
- To cooperate with government, academia, business, and industry in resolving important statistical issues which affect the health sciences.
- To develop standards of design, evaluation, and reporting of biochemical, biological human, and animal health experimentation.
- To assist in the development of curricula, training, and continuing education programs for statisticians supporting the health sciences.
- To participate in the development of the quantitative aspects of public policy concerning health products and services research.

- To serve as a resource for public and private groups or agencies with interests in the fields of human and animal health,
- To establish and maintain liaisons and cooperative efforts with other scientific and professional organizations.
- To participate in the discussion and examination of ethics related to human and animal experimentation.

Section Activities

Section Newsletter

The Section's newsletter, the *Biopharmaceutical Report*, presents information and a scientific interchange through articles, reviews, and discussions. It also publishes Section activities, information on upcoming events, meeting and workshop summaries, book and software reviews and awards announcements. The newsletter is published 2-3 times per year.

Sponsor ASA Sessions

The Section organizes invited and contributed presentation sessions, poster sessions, and roundtable discussions at the annual ASA meeting, the ENAR/ASA spring meeting, and the Winter Conference.

Co-sponsor Conferences, Symposia, Workshops, and Data Analysis Contests

Conferences, symposia, and workshops addressing the application of statistics to major topics in pharmaceutical research are co-sponsored by the Section. Examples are the annual Applied Statistics Conference and the Midwest Biopharmaceutical Statistics Workshop. Data analysis contests conducted by academia are supported by the Section.

Proceedings

The Section publishes a collection of papers presented at meetings that it co-sponsors.

Sponsor Tutorials and Short Courses

Section members develop and present statistical tutorials and short courses aimed at providing for continuing needs of professionals interested in the field of biopharmaceutical statistics.

Sponsor Work Groups and Task Forces

Section members interested in addressing particular statistical research problems or issues are sponsored and supported. Examples are the Population Pharmacokinetics Modeling Work Group and the Joint Task Force on Design and Analysis of Dental and Oral Research.

Liaison with Professional Associations

The Section maintains active liaisons with other health science professional organizations.

Best Presentation and Outstanding Paper Awards

In order to encourage better presentations, contributed papers in Section-sponsored sessions at the ASA Annual Meeting are judged for their overall presentation, and awards are granted for those judged best. Awards are granted to students for the best papers submitted for presentation.

ASA Fellow Nomination

The Section annually supports nominations of its members for award of ASA Fellow.

Section Benefits

- Participate in the effort to advance the use of statistics in therapeutic drug and device discovery, development, research, production, and regulation.
- Be part of a dynamic group that sponsors many activities and opportunities.
- Join an organized effort to increase association and cooperation with professional and technical groups with similar interests.
- Have the opportunities to actively participate in Section activities by joining committees or work groups, by participating in training programs or publication development, and by interacting with statisticians worldwide.

Biopharmaceutical

Organize invited, contributed, & poster sessions at the Annual Meetings
Organize roundtable discussions at the Annual Meetings
Arrange publication of proceedings from the:

- Annual Meetings
- ENAR/ASA spring meetings
- Midwest Biopharmaceutical Statistics Workshop
- Applied Statistics Conference

Produce the *Biopharmaceutical Report* newsletter (2-3 times a year)

Sponsor joint activities with other Sections and organizations

Sponsor short courses, tutorials, and workshops

Sponsor work groups and task forces

Co-sponsor statistical workshops and conferences

Present Best Presentation Awards for contributed papers

Present Outstanding Paper Awards to students at the Annual Meetings

Publish articles in *Amstat News*

Nominate Section members as ASA Fellows and provide supporting letters to nominations for ASA Fellow

Support data analysis contests conducted by educational institutions

Assist the FDA in identifying statisticians for Advisory Committees

Conduct intermittent membership surveys

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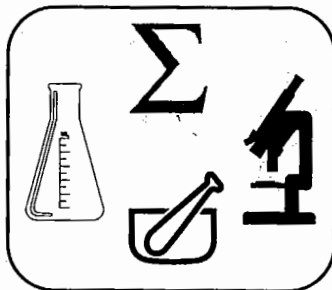
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