Estimands and Their Role in Clinical Trials

Mouna Akacha, Frank Bretz, David Ohlssen, Gerd Rosenkranz and Heinz Schmidli (Novartis)

Editors’ note: We’re pleased to present a feature article on estimands, motivated by the efforts of the ICH Expert Working Group addressing this topic, and in anticipation of the addendum to ICH-E9 that this group is preparing. This effort has been briefly alluded to in some of our recent issues, but given its interest to the section membership and its importance to our future practices, we wanted to highlight it further at this time. We look forward to the issuance of the addendum, and to providing further information on this important initiative in future issues.

Introduction and background
Scientific questions on medicinal products are often best addressed by randomized clinical trials. It seems obvious that the scientific question being addressed should drive trial design, conduct and analysis. However, oftentimes specific choices in the statistical analysis opaque re-define certain aspects of the scientific question, e.g. the measure of treatment benefit, which is clearly not appropriate.

An example where the measure of treatment benefit left room for ambiguity was discussed in 2011 in a public advisory committee meeting. Astra-Zeneca and Bristol-Myers Squibb presented data on their anti-diabetic drug dapagliflozin [1]. The primary endpoint for
their pivotal studies was the change in glycated hemoglobin (HbA1c) from baseline to 24 weeks. Throughout the studies, patients received glucose-lowering rescue medications for the remainder of the trial, if one of several markers of glycemic control exceeded pre-specified thresholds. The statistical analyses included all randomized patients who received at least one dose and for whom the HbA1c baseline value and at least one postbaseline value were available. Measurements collected after initiation of rescue medication were set to missing. This appears to be common practice in the analysis of diabetes trials, as intake of rescue medication may mask differences in glycemic values between treatment groups, especially as it will occur more frequently in less effective treatment groups. Following the tradition at the time, the last pre-rescue-medication value was carried forward and analyzed as the end-of-trial value.

The statistical reviewer at the FDA commented on the primary analysis using the last observation carried forward (LOCF) approach as follows [1]:

“While FDA has implicitly endorsed LOCF imputation for diabetes trials in the past, there is now more awareness in the statistical community of the limitations of this approach. […] My own preferred analysis simply uses the observed values of patients who were rescued. This approach may seem counterintuitive if one believes that rescue treatment makes the subsequent outcomes less relevant to evaluation of the test agent. It has the virtue, however, of respecting the intent-to-treat principle, in the sense that the analysis is based on the randomized treatment rather than the treatment actually received (i.e., planned treatment plus rescue).”

At first glance it seems that both parties have simply used a different statistical approach to analyze the data. On the one hand, the sponsors removed the data after initiation of rescue medication and applied the LOCF approach to impute the resulting missing data. On the other hand, the FDA statistician refrained from using LOCF due to the poor statistical properties and included all data regardless of initiation of rescue medication.

But the implication of using a different statistical approach to analyze the data goes far beyond statistics. The implied scientific questions of interest that are answered by the two parties are fundamentally different. The sponsors seem to be interested in establishing the treatment effect of the initially randomized treatments had no patient received rescue medication, while the FDA statistician is comparing the treatment policies ‘dapagliflozin plus rescue’ versus ‘control plus rescue’.

As shown in this example, differences in the scientific question may arise due to different ways of handling data after study treatment discontinuation or intake of rescue medication, although this ambiguity may not be clear to the clinicians or statisticians involved in the trial, neither on the sponsor nor on the regulatory side.

**The need for change**

The current practice of defining trial objectives vaguely creates various challenges which should be averted. Instead of approaching the issue of estimation from an analysis point of view, it is preferable to go back to first principles and to clearly define what is to be estimated, leading to the concept of an *estimand*. When there is agreement on the scientific question of interest, or in other words ‘that which is to be estimated’ the appropriate study design, data capture and analysis should be evident.

At first glance this seems obvious; however, more often than not, current practice fails to state the primary objectives in a precise way. As seen in the dapagliflozin example, many trials even leave ambiguity as to how treatment benefit is assessed. The resulting confusion, especially in the context of missing data, has led to regulatory challenges in the past. This raises the need for more transparency and clarity regarding the scientific question of interest posed by a trial, as highlighted, for example, in the National Research Council (NRC) document ”The Prevention and Treatment of Missing Data in Clinical Trials” [2]. While this document focuses on issues arising due to missing data, the need for a structured framework to specify the scientific question of interest applies to a broader setting.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has reinforced the need to more clearly distinguish between the target of estimation (‘estimand’) and the method of estimation (‘estimator’) through the publication of a concept paper [3] in October 2014. Besides estimands, the concept paper also discusses the role of sensitivity analyses. Since then a working group has been tasked to develop a corresponding addendum to the ICH E9 guidance document [4] - the main statistical guidance in drug development adopted globally by regulatory bodies and followed by the pharmaceutical industry.

**Framework for planning, conducting and interpreting analyses of clinical trials**

The key objective of defining estimands is to bridge trial objectives with proper inference tools in a transparent
Remarks

Trial Objective
- Derived from informative Target Product Profiles and/or Clinical Development Plans

Estimand
- Derived from the trial objective and driving the clinical trial design

Estimator
- A single primary estimator (ultimately defining the primary analysis for the given estimand), possibly in conjunction with multiple (say k) sensitivity estimators (still linked to a same estimand, but varying assumptions)

Estimate
- For each (primary, sensitivity) estimator, derive an associated (primary, sensitivity) estimate and measure of uncertainty based on the available data

**Figure 1**: Structured framework bridging trial objectives with proper inference tools.
and coherent way; see Figure 1. Loosely speaking, an estimand is closely linked to the purpose or objective of a clinical trial. It describes what is to be estimated based on the question of interest and can be defined through the

- Population of interest (reflected through the inclusion/exclusion criteria of a given study);
- Endpoint of interest (measurement and time point/period of interest);
- Measure of intervention effect (taking into account the impact of post-randomization events such as intake of rescue medication, discontinuation of study treatment, dropout etc.).

In contrast, an estimator defines the specific rule according to which the estimand is to be estimated - assumptions will typically have to be made when defining the specific estimator. For this reason, it is logical to conduct a sensitivity analysis which should be a structured and targeted sequence of analyses and thus estimators to investigate the robustness of the primary estimator for a given estimand to model assumptions and data limitations.

The framework depicted in Figure 1 thus helps in distinguishing between the target of estimation (trial objectives, estimand), method of estimation (estimator, estimate, measures of uncertainty), and sensitivity analysis. Especially in the context of ‘missing data’, estimand and method of estimation are often confused. However, as mentioned before, the estimand framework applies to a broader setting than missing data.

**Potential impact on our work**

Generally, the new estimand framework will require us to define more clearly what we want to assess. The appropriate analyses will become a logical consequence of this definition, whereas today there is a tendency to start thinking about analyses and imputation schemes first and ponder afterwards what they entail. Thinking about the impact of post-randomization events such as treatment discontinuation or missing data at the trial design stage and choosing appropriate approaches to handle these means our conclusions will stand on firmer ground which should help us better understand treatment benefits and present a stronger case to regulators.

The identification of appropriate estimands at the design stage will require more informed discussions with all stakeholders involved, i.e. clinical teams, regulatory agencies, payers and patients. Importantly, the choice of estimands will drive the trial design, protocol language, trial conduct and statistical analyses; see also the NRC document [2] for several examples of the interplay between estimands and trial designs.

Certain estimands may even require innovative designs and endpoints - thus also new statistical methodologies and potentially new clinical guidance documents may need to be developed.

The current efforts in this area are part of a process that has potential to broaden and enhance long-established paradigms and conventions, to improve the meaningfulness of clinical trial results for all parties involved. This is thus a very exciting time to be a statistician working in pharmaceutical development – stay tuned!

**References**


ASA Biopharmaceutical Section Statistics Workshop Recap

Wei Zhang and Richard Zink

The 2015 ASA Biopharmaceutical Section Statistics Workshop was held September 16-18 in Washington D.C. Approximately 830 FDA, academic and industry colleagues gathered to share insights into key trends in statistical topics relevant to medical product development. Wei Zhang (FDA/CVM) and Richard Zink (JMP Life Sciences, SAS Institute) co-chaired the meeting. Together they led a Steering Committee, made up of FDA, industry and academic representatives, to develop an informative program that included 8 half-day short courses, more than 50 roundtable discussion topics, and 42 parallel sessions on a large variety of topics including, but not limited to, Bayesian methods, benefit-risk, biomarkers, cardiovascular safety in type II diabetes, CMC, data standards and transparency, estimands and sensitivity analysis for missing data, generics and biosimilars, incorporating patient perspectives, medical devices and diagnostics, patient enrichment, statistical leadership, subgroups, and methodologies for vaccine and veterinary development.

In his 2015 State of the Union address, President Barack Obama announced a precision medicine initiative with a goal “to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized treatments” [1]. In the spirit of this initiative, the workshop began with plenary presentations and panel discussion on the Future of Precision Medicine. In the first session, Lisa LaVange (FDA/CDER) summarized Precision Medicine Initiatives at FDA, and Susan Murphy (University of Michigan) discussed Micro-Randomized Trials and mHealth. In the second session, LaVange and Murphy were joined by Cong Chen (Merck), Greg Campbell (formerly of FDA/CDRH), Estelle Russek-Cohen (FDA/CBER) and Richard Simon (NCI) to address prepared and audience questions on precision medicine. The co-chairs especially want to thank Christina Link, ASA Meetings Planner, and the ASA staff for their tremendous efforts in coordinating the workshop logistics. Without the contribution of all, this successful meeting would have not been possible.

Wei and Richard are very grateful for the support from all who participated, including the Steering Committee members, session organizers, chairs and speakers, short course presenters and Workshop participants. The call for proposals will open soon! Ready your proposals and abstracts for parallel sessions, town halls, roundtable topics, and short courses.

Reference

www.whitehouse.gov/precision-medicine
According to Wikipedia, “Volunteering is generally considered an altruistic activity where an individual or group provides services for no financial gain. Volunteering is also renowned for skill development, and is often intended to promote goodness or to improve human quality of life. Volunteering may have positive benefits for the volunteer as well as for the person or community served. It is also intended to make contacts for possible employment.”

JSM 2015 in Seattle was the second year of ASA’s Docent Program for the Joint Statistical Meetings and the first year that the Biopharmaceutical Section (BIOP) selected this project for Section members to volunteer a little of their time in service to the ASA and to first-time JSM attendees.

As a bonus to 2015 Section volunteers, the BIOP Executive Committee agreed to purchase for each volunteer a polo-type shirt branded with our Section the BIOP JSM Docents!

BIOP “Sets the Bar High” with Docent Volunteers

B. Christine Clark and Theodore C. Lystig (Medtronic, Inc.)

The activity provided an opportunity for BIOP members at JSM to

1) help others
2) get more involved in ASA and BIOP activities
3) learn more about all that JSM offers
4) raise the visibility of BIOP among attendees
5) meet fellow statisticians including some already in BIOP or potential new BIOP members
6) network with colleagues. More than one ASA leader stated that BIOP “set the bar high” for all Docent volunteers, with such a strong showing in number and quality of Section members volunteering their time in service to others through this program.
name and logo. In addition to the badge ribbons that all Docents wore throughout JSM, the special shirts worn during the Sunday afternoon orientation session and the Tuesday evening BIOP Open Mixer and Business Meeting helped to make the BIOP Docents readily identifiable to first-time attendees. The shirts also functioned as a form of mobile advertising for BIOP.

Feedback regarding their Docent experience was consistently positive from the 21 BIOP members who volunteered. Much of the positive feedback involved anecdotes from the first-timer orientation luncheon in which the Docents participated as table leaders. One first-time attendee, an academic, asked the BIOP Docent seated at his table what types of academic skills/courses were most valuable for students to be attractive as new hires when they graduate. What a great opportunity to have a potential impact on graduate programs to ensure the supply of well-prepared future statisticians! At another table during the Sunday afternoon orientation, a statistician who had attended previous JSMs accompanied a “first-timer” to the orientation. When the Docent encouraged those at her table to attend the open business meeting of any Sections in which they were interested, e.g., the BIOP Open Mixer and Business Meeting on Tuesday evening, the previous attendee spoke up and said he had no idea that these open business meetings could be attended by all Section members or by those who wanted to know more about a particular Section.

On behalf of the BIOP Executive Committee, thank you to the 21 members who volunteered their time in service to the ASA and to the Section as BIOP Docents at JSM 2015 in Seattle. Please extend your own thanks and ask them about their experience as Docents. You might decide this is an activity for which you would like to volunteer at next year’s JSM in Chicago, 30 Jul – 04 Aug 2016.

**BIOP Docents at JSM 2015 in Seattle**
(in alphabetical order):
Vipin Arora, Fred Balch, Janelle Charles, Christie Clark, Jennifer Gauvin, Ofer Harel, Kuolung Hu, Amarjot Kaur, Ted Lystig, Joel Michalek, Sharon Murray, Veronica Powell, Dionne Price, Junshan Qiu, Matt Rotelli, Matilde Sanchez-Kam, Heather Thomas, Nancy Wang, Mei-Miau Wu, Guan Xing, Ming Zhou. All three major categories of employment (industry, government and academia) were represented, in a ratio of approximately 5:1:1.

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**2016 CONFERENCE ON STATISTICAL PRACTICE**

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International Initiatives Subcommittee Report: 
ICH E9(R1) as an Example of a Successful International Collaboration

Frank Bretz, Novartis

This is the third in a series of reports from the Biopharmaceutical Section International Initiatives Subcommittee, with perspectives spanning the different regions represented by its members. Brian Wiens [1] described this new project, its objectives, and the subcommittee membership representing three major geographic regions. Toshimitsu Hamasaki [2] illustrated global collaboration by means of the Austria-Japan Joint Statistics Workshop on “Innovative Clinical Trial Designs and Personalized Medicine for Accelerating Medical Product Development”, hosted in late March 2015 in Osaka, Japan. His report ended with a call for proposal of an Invited or Topic Contributed Session tentatively entitled “Global Challenges, Global Collaboration in Biopharmaceutical Statistics” at JSM 2016 in Chicago. In this article I will provide another example of international collaboration by giving an update on ICH E9(R1), as considerable progress has been achieved since Thomas Permutt first described this activity in the Winter issue of the Biopharmaceutical Report [3].

As a brief reminder, the main goal of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is to promote international harmonization by bringing together representatives from regulatory agencies and pharmaceutical industry to discuss and elaborate common technical guidelines with the aim to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. The ICH’s series of “E” guidance documents (E = Efficacy) includes E9 which covers the statistical principles that apply to the analysis of clinical trials and is essentially the main statistical guidance in drug development adopted globally by regulatory bodies and followed by pharmaceutical industry. Last year, ICH called together an Expert Working Group (EWG) to develop for this document an addendum on estimands and sensitivity analyses for improved clinical trial planning, conduct, analysis and interpretation.

The EWG consists of regulatory and industry representatives from Europe (EMA, MHRA, EFPIA), Japan (MHLW/PMDA, JPMA), US (FDA, PhRMA) and other regions (ANVISA, Brazil; HC, Canada; TFDA, Taiwan), with Rob Hemmings (MHRA) being the rapporteur and Estelle Russek-Cohen (FDA) the regulatory chair. The EWG met in person twice during the past 12 months (Lisbon, Portugal in November 2014, and Fukuoka, Japan in June 2015), with monthly teleconferences covering the time span between the face-to-face meetings. The EWG quickly agreed on the scope of the E9 addendum to present a structured framework to bridge trial objectives with proper inference tools, permitting more coherent inference and decision making. The focus is on the principles that allow defining an estimand and a structure for identifying sensitivity analyses. In the meantime, the work of the EWG has been brought forward and presented in public to stimulate the discussion around this topic, such as at the JPMA Symposium (Tokyo, February), DIA-FDA Statistics Forum (Washington DC, April), PSI Annual Meeting (London, May), ISBS (Beijing, June), JSM (Seattle, August), ASA Biopharmaceutical Section Statistics Workshop (Washington DC, September), EFSP/PSI One-Day Meeting (London, September), DIA Japan Annual Meeting (Tokyo,
November), among others. A related survey conducted by the EWG and facilitated by the ASA Biopharmaceutical Section had more than 1300 responses from around the globe.

To me, this increasing public discussion on estimands and sensitivity analyses is a wonderful testimony for how statisticians involved in drug development, coming from different regions and working in different environments, can collaborate productively at the highest scientific level. The next face-to-face meeting of the EWG is scheduled for December in Jacksonville, US, by which time the Technical Document is expected to be finalized. While I look forward to further discussions following its release for public comments soon thereafter, I will certainly also miss the work and the collaborative atmosphere within the EWG itself once the addendum has been finalized. In his report after the Lisbon meeting, Thomas Permutt wrote: “We debated, we listened, we harmonized. I learned and I taught” [3].

I could not agree any more, except for a tiny extension of his statement: I learned and I taught, too. We all learned and taught!

References
71st Annual Deming Conference on Applied Statistics
Registration Now Open!

American Society For Quality:
NY/NJ Metropolitan Section & Statistics Division
American Statistical Association:
Biopharmaceutical Section

When and where: December 7 – 11, 2015. Tropicana
Casino and Resort, Havana Tower, Atlantic City, NJ

Reduced Registration Fee for Students and Retirees; One
Day Registration Also Possible Registrants May Submit
Poster Abstracts for Approval by Conference Committee
Early registration deadline October 1

Editor’s Note: Walter Young has written an entertain-
ing article reminiscing on his 45 year tenure as chair-
man of the Deming Conference on Applied Statistics. He has also created an Excel file containing all speak-
ers, topics and moderators for all tutorials and short
courses for the past 27 years. Both of these documents
can be downloaded from www.demingconference.com.

Conference program
Three hour conference tutorials, Monday – Wednesday

Doing Bayesian Analysis Using PROC MCMC*
Fang Chen, SAS Institute

Multiple Testing for Correlated Multiple Endpoints
in Clinical Trials*
Changchun Xie, University of Cincinnati; Din Chen,
University of Rochester

Design Issues in Biomarker-Based
Clinical Trials in Oncology
Daniel J Sargent, Mayo Clinic

Applying Bayesian Evidence Synthesis In
Comparative Effectiveness Research
David Ohlssen, Novartis

Statistical Methods for Tailored Therapies
in Pharmaceutical Drug Development
Lei Shen, Eli Lilly

Sensitivity Analysis for Missing Data Using Bayesian
and Imputation Approaches - Case Studies from DIA
Bayesian Working Group
Frank Liu, Merck & Neal Thomas, Pfizer

Graphical Approaches to Multiple Testing*
Dong Xi, Novartis

Statistical Methods for Medical Product Safety
Evaluation
Jie Chen, Novartis; Mei-Chiung Shih,
VA Cooperative Studies Program & Stanford University

Propensity Score Methods for Estimating Causal
Effects In Non-Experimental Studies: The Why,
When, and How
Elizabeth Stuart, Johns Hopkins

Advanced Statistical Concepts and Methodologies
For Development of Personalized Medicines
Cong Chen, Merck

Design and Analysis of Non-Inferiority Trials*
Brian Wiens, Portola Pharmaceuticals

Network Based Analysis of Big Data
Shuangge Ma, Yale University

Courses, Thursday – Friday
Quantitative Evaluation of Safety and
Benefit Risk In Drug Development
Larry Gould, William Wang & Weili He, Merck;
Qi Jiang; Amgen Inc.

Propensity Scores and Matching,
with Implementation in R
Ben Hansen, Ed Rothman & Josh Errickson,
University of Michigan

* Session is based on a text that will be sold at a substantial discount at the conference.
Report from the BIOP Membership Committee

Jennifer Gauvin, Matthew Guerra, Soumi Lahiri

Fellows listing
Released this year! - an updated listing of your fellow Biopharmaceutical Section members who are ASA Fellows, searchable by year: http://community.amstat.org/biop/aboutus/asafellow. Each fellow’s name is a clickable link that will take you to their ASA profile. In 2015, nine of the new fellows are members of the Biopharmaceutical Section (and congratulations to those individuals! - Girish Aras, Raymond Bain, Bruce Binkowitz, Frank Bretz, Susan Halabi, Ofer Harel, Gang Li, Robert Small, Abdus Wahed).

Profile updates
We encourage members to edit their ASA profiles, and share as many or as few details about yourself as you’d like. You can include your picture to meet and network with others in ASA.

Consider updating your e-mail address and ASA profile on a yearly basis. Make it your New Year’s resolution! It’s an easy action to complete in January. Encourage your colleagues to be sure to update their address.

Survey
In order to better serve the BIOP section membership, the Membership Committee conducts a survey every three years to collect information regarding demographics, education, professional experiences, professional meetings and continuing education activities, and career development, as well as to obtain feedback and suggestions from the members on the services provided by the section.

The first survey was conducted in 1996 and consisted of a 41-item questionnaire that was mailed to section members. The cost for the preparation and mailing of the survey was $4,620 and the cost of the T-shirts (an incentive for filling out the survey) and mailing was $8,146, for a total cost of $12,766. The second survey conducted in 2009 was the start of triennial surveys; however, after realizing that outsourcing the implementation, conduct and analysis of the survey was beyond the allotted budget, the committee implemented a do-it-yourself approach, transitioning from a paper survey to a web-based survey (i.e., surveymonkey.com).

The 2015 survey was conducted between July 22 and August 28. As an incentive, individuals who completed the survey received complementary access to an ASA webinar of their choice. The results of the survey will be published in the next issue of the Biopharmaceutical Report.
The International Society for Biopharmaceutical Statistics (ISBS) held, together with DIA-China, its 4th international symposium on biopharmaceutical statistics in Beijing, China, from June 29 – July 1, 2015. ISBS was founded in 2008 by a group of statisticians in the pharmaceutical industry and held its first symposium in Shanghai in 2008. The second symposium was jointly hosted with the European Medicines Agency and the German Region of the International Biometric Society in Berlin in 2011. The third ISBS symposium was held in Washington DC in 2013, together with the International Chinese Statistical Association annual conference.

The 2015 ISBS-DIA Joint Symposium was attended by approximately 350 registered participants from academia, government regulatory agencies and the biopharmaceutical industry from over 20 countries or regions. As in previous meetings, we were delighted to have so many participants including members of the ASA Biopharmaceutical section attending the symposium in Beijing this year.

This year’s symposium featured six pre-symposium short courses, two keynote speech sessions, three plenary panel discussion sessions, and 53 invited and contributed parallel sessions, with a total of 212 presentations covering a variety of topics from visionary and strategic thinking, regulatory activities and perspectives, to statistical theory and applications in biopharmaceutical research, development, regulation, and product life-cycle management; see www.isbiostat.org/sp4 for details of the program.

At the opening keynote session, Robert Hemmings of the Medicines and Healthcare Products Regulatory Agency (MHRA) of UK shared his views on statisticians supporting the next era of medicines’ development; and Lee-Jen Wei of Harvard University discussed “Can we make statistical analysis of a clinical study more transparent for clinical practice?” In the second keynote session, Zhi’ang Wu of Shenyang Pharmaceutical University presented the challenges and opportunities for drug development in China; and Yuki Ando of the Pharmaceutical and Medical Device Agency (PMDA) of Japan shared with the audience the current and future activities for statistical review of new drug applications in Japan.

Also highlighted were three plenary panel discussion sessions on regulatory, methodology and industry questions. The regulatory panel session, moderated by Frank Bretz (Novartis) on day 1, included Yuki Ando (PMDA), Robert Hemmings (UK MHRA), Franz Koenig (Medical University of Vienna), Yi Tsong (US Food and Drug Administration, FDA), Marc Walton (Johnson & Johnson) and Jielai Xia (China’s 4th Military Medical University). Topics discussed in the regulatory panel session consisted of regulatory challenges and opportunities including applications of innovative statistical design and analysis methods, and regulatory perspectives on handling regional differences and similarities in multi-regional clinical trials. The methodology panel session on day 2, moderated by Dejun Tang (Novartis), included Loic Darchy (Sanofi), Joe Heyse (Merck), Peter Mueller (University of Texas), Jose’ Pinheiro (Jansen), Stephen Senn (Luxembourg Institute of Health), and Jeremy Taylor (University of Michigan). The methodology panelists shared their views on statistical methodology research for quantitative benefit-risk assessment, multi-regional clinical trials, and big data, as well as the implications for drug
development and regulation. The industry leadership panel session, moderated by Ivan Chan (Merck), on day 3 comprised Vladimir Dragalin (Johnson & Johnson), Pandu Kulkarni (Eli Lilly), Marcia Levenstein (Pfizer), Thorkild Nielsen (Bayer), Nicole Li (Roche), Martin Roessner (Parexel International), Jerald Schindler (Merck), and Frank Shen (AbbVie). The industry leadership panelists shared their perspectives on statistical innovation in adaptive clinical development, biomarker strategy, personalized medicine and tailored therapies, as well as predictive analytics/big data, and the leadership roles of statisticians in the research, development, regulation and life-cycle management of biopharmaceutical products.

During the two days before the main events, the symposium also offered short courses on adaptive designs, multiple testing, sequential analysis and experimentation, Bayesian statistics and computation in clinical trials, benefit-risk analysis, and equivalence and similarity testing.

The ISBS plans to hold its next biennial symposium in 2017 - so please watch the ISBS website (www.isbiosstat.org/) for future announcements. As an international organization, the ISBS appreciates all sponsorships and welcomes all statisticians worldwide (e.g., ASA Biopharm Section members and other colleagues) to join its effort. If you are interested in joining the effort, please write to: Info@IsBioStat.org.

**Calling All Volunteers!**

Want to get involved in Biopharm Section activities, but not sure how? The Section is always looking for volunteers, so drop us an e-mail at volunteer.asabiopharm@gmail.com.

**Let’s Hear from You!**

If you have any comments or contributions, please contact the Editors: Jerry Wang, email jerry.wang@merckgroup.com; Ugochi Emeribe, email ugochi.emeribe@astrazeneca.com; or Paul Gallo, email paul.gallo@novartis.com. We are looking for volunteers to write articles or suggest topics that will be of interest to our members. The topics can be technical, but non-technical articles related to biopharmaceuticals are welcome. Please send us an email.

The *Biopharmaceutical Report* is a publication of the Biopharmaceutical Section of the American Statistical Association.
The fourth U.S. conference dedicated entirely to nonclinical biostatistics topics will take place in Driscoll Hall on the campus of Villanova University. Members of the nonclinical /preclinical Statistics community are invited to submit proposals for presentations and posters discussing significant scientific and regulatory issues. Attendees will have ample opportunity to network, share experiences and discuss current scientific issues with colleagues and leaders in the field.

Abstract submission and registration is through the conference website [www.ncb2015.net](http://www.ncb2015.net). Contributed presentation abstract/poster submission cutoff date is June 26, 2015.

Nominations for Outstanding Nonclinical Paper Award being accepted.

**Keynote speakers on Tuesday October 13:**
- **David Morgenstein**, ASA President 2015
- **Lisa Lavange**, Director of the Office of Biostatistics, FDA

Choice of half-day short course:
- Statistical Methods in Drug Combination Studies (Harry Yang, MedImmune)
- Applied Bayesian Statistics for Nonclinical (David LeBlond, Consultant)

21 Invited or contributed presentations covering:
- Discovery/Biomarkers – John Peterson, Matthew Nelson, Michael Wu
- Safety/Pharmacology – Dan Holder, Steve Bailey, Dhammika Amaratunga
- CM&/C/Manufacturing – Yi Tsong, Helen Strickland, Celia Cruz, Lori Pfahler, Kim Vukovinsky

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*The Biopharm section of the ASA is a contributing sponsor of the conference.*