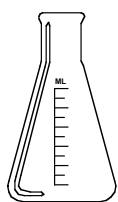


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## Common Challenges Facing Statisticians In Nonclinical Biostatistics

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### 1. Introduction

At the 1998 ASA Joint Statistical Meetings in Dallas, the ASA Committee for Applied Statisticians sponsored an invited panel session entitled, "Doing Statistics in a Non-Statistical World: Common Challenges Facing Applied Statisticians." Of the four statisticians on the panel, I was the only member working in the pharmaceutical industry. Prior to the meeting, the organizers of the session gave the following five questions to the panel members. Each panelist addressed one or more of the questions in his presentation.

1. How can statisticians convey the importance of statistical input at the design stage?
2. How can statistical concepts be explained without jargon?
3. What background should be required for a statistician in an application area?
4. How much time should be spent on training scientists?
5. How can statisticians get scientists to think like statisticians?

My approach to responding to these questions was to conduct a survey of non-clinical statisticians (i.e., any statistician who does not analyze clinical trial data) in the pharmaceutical industry. Included in the survey were the five questions listed above as well as a sixth question, "What do you feel is the most common challenge for statisticians?" This article presents the results of the survey as well as some personal comments on the six questions. Since non-clinical statisticians collaborate with scientists during all stages in a compound's development, a brief description of these stages is given in the following section.

### 2. Stages of Drug Development

In general, the drug development process starts with synthesis/extraction of a compound and ends with the approval of the dossier by the regulatory agency. The main components of this development process, as defined by the Pharmaceutical Research and Manufacturers of America (PhRMA), are: Synthesis and Extraction, Biological Screening and Pharmacological Testing, Toxicology and Safety Testing, Pharmaceutical Dosage Formulation and Stability, Clinical Evaluation Phases I, II, and III, Process Development for Manufacturing and Quality Control, Regulatory IND & NDA, and Bioavailability. The PhRMA also adds Clinical Evaluation - Phases IV and Other as two additional components to provide yearly information on the allocation of domestic US research and

## Contents

### FEATURED ARTICLE

Common Challenges Facing Statisticians in Nonclinical Biostatistics .....	BERGUM	1
Discussion .....	HAJIAN	5
Discussion .....	HUBER	6
Discussion .....	ARSEVEN	7

### BIPHARMACEUTICAL SECTION NEWS

Letter from the Chair .....	SNAPINN	9
Electronic Mailing List .....	GREENBERG	10
Section Web Site .....	GHOSH	10
FDA/Industry Workshop .....		11

development expenditures by function. Based on the latest information (1996), more than 50 percent of the Research and Development (R&D) resources in the USA are consumed by the nonclinical area. As indicated by the percentage of the allocated R&D funds and the number of main components of drug development it encompasses, the nonclinical area is large and scientifically diverse.

The main components described above by PhRMA can be grouped into two broad stages – Discovery and Development. The third and final stage is Manufacturing. These three stages are described in the following sub-sections.

### Discovery

The primary goal of drug discovery is to find compounds that are active against meaningful targets (e.g. receptors on proteins, enzymes, cells, or genes). Discovery also performs basic research to understand the underlying mechanisms. Discovery scientists come from a variety of different fields, including molecular biology, medicinal chemistry, genetics, combinatorial chemistry, and pharmacology. Traditionally, scientists have used human diseases as indicators to identify potential disease targets. Some of the new techniques include using knock out mice and looking for over-expression of proteins. To find new compounds, scientists screen compounds from internal chemical synthesis or natural product libraries or from commercially available libraries. New technologies, such as high-throughput screening (HTS), are used to quickly screen the growing number of compounds. If screening provides a “hit,” the compound is “optimized” to improve activity. Once the compound has been optimized, pharmacologists may study the compound in an animal model. A relatively new area in discovery is Genomics. Genomic libraries have been generated that are being studied to try and understand a particular gene, its pathway and function. Nonclinical statisticians are involved in finding ways to identify targets quicker, screen compounds faster, more effectively examine information in large databases, and improve assay methods. These tasks provide many statistical and data management challenges.

### Development

Once a compound shows desirable activity, a company decides whether or not to begin the development stage. In this stage, the goal is to show that the drug is safe and effective. However, there are many other goals to achieve. This includes finding a formulation that can be given to humans, finding a delivery route, stabilizing the formulation and scaling up to production quantities. The two target events during the development process are the IND (Investigational New Drug) and the NDA (New Drug Application). Approval of the IND by the FDA allows the compound to be used in humans so that clinical trials can begin. Some of the information required in the IND are drug composition, synthesis process (or extraction method), animal toxicology, short-term stability, and the phase 1 protocol. During the time point between the IND and NDA, the company will develop a formulation, conduct long-term stability studies, complete animal reproductive toxicology and carcinogenicity studies (if needed), perform clinical studies, develop assay methods and improve the drug synthesis. Once the company believes that

the compound is safe and efficacious, the information from all these activities is compiled into an NDA and sent to the FDA. Although the majority of statisticians in the pharmaceutical industry are involved in the clinical trial area, many companies also have a nonclinical statistics group that collaborates with scientists during development. The most common areas in which statisticians work are animal drug safety and stability studies. In many companies, they are also involved with screening and optimization experiments for formulation and drug synthesis, analytical method development, and specification setting.

### Manufacturing

Once the FDA approves the NDA, the product is transferred to manufacturing. The first production batches are used for process validation where the company must show that the process does what it purports to do. Various tests are performed. These include content uniformity and dissolution to show that the granulation is uniform throughout processing and that the final product has acceptable dissolution rates. Once the process has been validated, the Quality Control department monitors future batches to make sure that the process remains in control. Quality Control statisticians are involved with providing sampling plans, developing internal guidelines and release specifications, problem batch resolution, and monitoring stability.

### 3. Survey Results

The statisticians chosen for the survey were not picked randomly but rather chosen from statisticians I've met over the years. They were asked to pass the survey on to others. Thirty responses from the nonclinical statisticians of the thirteen major pharmaceutical companies were received. There are probably about 150-200 nonclinical statisticians in the pharmaceutical industry, so perhaps 20 percent of all nonclinical statisticians were included in the survey.

The results for each question are given below with the frequency for each listed response, a summary of written responses and personal comments.

- 1) How can statisticians convey the importance of statistical input at the design stage?

Listed Responses	Frequency
Provide DOE Training	24
Use Published Examples	16
Give Examples of Poor Designs	12
Wait For a Poor Design	6

The survey indicates that design of experiments (DOE) training is the best way to convey the importance of statistics at the design stage. The most common written responses were getting management support and more exposure by promoting statistical thinking, finding champions, giving joint presentations, writing a newsletter, showcasing experiments, interacting with scientists, and advertising. To better convey the importance of statistical input, I think that the scientists need to be aware of what a statistician can offer. Most data is probably collected and examined by scientists without statis-

tical input because the scientists are unaware of how a statistician can help.

2) How can statistical concepts be explained without jargon?

Listed Responses	Frequency
Use Examples in the Application Area	23
Use Hands-On Experiments	18
Use Everyday Examples	13
Provide Formal Training (Only if asked)	8
Provide Formal Training (We decide)	8

The survey indicates that the best way to communicate is by using examples in the application area. Written responses agreed, suggesting the use of simple relevant examples in the scientist's language. I agree. Most scientists don't want to be statisticians and don't want to know a lot of statistical jargon. They want to have a study that is well designed with the results that are interpretable. They trust that the statistician will help them do this. Part of consulting is to determine how much jargon is necessary to communicate with the scientist and how much the scientist needs to know to communicate with others. We need to "read" the scientist to determine when he or she is getting lost or losing interest. A certain amount of jargon may be necessary since the scientist may use software that contains jargon.

3) What background should be required for a statistician in an application area?

Listed Responses	Frequency
Train on the Job	18
Enough to Feel Their Pain	13
None: Learn from Scientist	5
Enough to Develop Statistical Model	3
None: Just Statistics	1
Need Formal Degree	1
Varies With Research Area	1
None: Learn from Statisticians	1

The survey results indicate that statisticians don't think that a formal degree in the application area is required. However, statisticians should train on the job by learning from the scientists, attending seminars, reading on their own, etc. The statistician should know enough to "feel the scientist's pain." The written responses agreed that some background is helpful but not necessary. I think that since nonclinical statisticians work with a wide variety of scientists and projects, it's not necessary that a statistician have a degree in associated non-statistical areas. If the statistician was dedicated to a specific application area, then requiring background in that area would make sense. The ideal person is someone with a broad scientific background, who has the enthusiasm and desire to learn from the scientists, attends seminars or short courses, and reads on his own.

4) How much time should be spent on training scientists?

Listed Responses	Frequency
Give Short Courses	18
Give Occasional Seminars	16
One on One	8
Use Outside Speakers	8
Lots of Training So Scientists can do it on Their Own	6
Lots of Training to Use Statistical Software	1
No Training: It's the Statisticians Job	0

The survey indicates that statistical training should be in the form of short courses and occasional seminars. The written responses were highly variable, with suggested time for training ranging from five to 50 percent. Of course, we get involved with training whenever we discuss the design or go over the analysis. Training works better when scientists ask for training rather than when the statistician tells them they need training. The concern I have with training is the false sense of success that training provides for both the instructor and students. When the course is over, the students and instructor are energized. Everyone thinks that the course was great. However, a month later, all that is remembered is that the course was great. In order to have success, follow up is required. The students need to use what they have learned and the instructor needs to get involved with the students once the course is over. One of the problems with bringing in courses from the outside or taking a course outside the company is that there is much less opportunity for follow up.

5) How can statisticians get scientists to think like statisticians?

Listed Responses	Frequency
One-on-One Interaction	26
Training Courses	21
Review Their Reports	15
Provide Software	14
Bring in Speakers	8

The survey indicates that the best way to make scientists think like statisticians is one-on-one interaction or training courses. Written responses included becoming part of the team, reviewing protocols, and starting discussion groups. One comment was that we should not expect scientists to think like statisticians. To a certain degree, I agree. We spend two to eight years training to be statisticians and have years of experience and yet expect scientists to think like statisticians. At best, statisticians would like scientists to understand and be concerned about some of the issues we are concerned about, such as confounding, randomization, etc. Perhaps the best way to get them to think like statisticians is to let the scientists see statisticians "think." We need to interact with the scientists more often. We should explain to the scientists why we are ask the questions we ask, why we chose particular plots, etc. We need to attend their meetings, become more active in their professional societies, and review their professional journals.

## 6) What is the most common challenge for statisticians?

Listed Responses	Frequency
Becoming a Valued Team Member	21
Dealing With Shortened Timelines	17
Getting Upper Management Support	13
Improving Our Image	5
Becoming Programmers	2
Finding Statistical Software	0
Increased Outsourcing	0

The survey indicates that the most common challenge for statisticians is to become a valued member of the team and learning to deal with shortened timelines. The written responses included dealing with large data sets, getting our foot in the door, keeping up with changes in science and technology, teaching upper management to be better statistical thinkers, contributing to the bottom line, and staying in the loop throughout the project. I think that we need to find a way to fit and have impact in this fast-paced environment. If scientists don't have time to perform traditional factorial designs, statisticians need to find other approaches. Statisticians are trained to have "data smarts" and be problem solvers. These are skills that can help the scientist to do better science.

Another challenge for a statistician is dealing with data that is not readily available, such as out sourced studies and "black box" software used by the scientists. This makes it difficult for the statistician since the information needed to solve problems is not accessible. Statisticians also need to become flexible and look for new areas where statistics can have an impact. Statisticians need to expand their roles to fit into the new environment. They need good people skills, team skills, management/leadership skills, etc.

#### 4. Factors Influencing Survey Results

Three factors, in my opinion, that influence how a non-clinical statistician responds to the survey questions are discussed below. They are the effect of government regulation, changes in the work environment, and the type of projects performed versus the statistician's interest.

##### Regulation:

One of the main differences between the pharmaceutical industry and other industries is the degree and extent of government regulation, particularly "standard" analysis and auditing. The FDA issues guidelines on how to design and/or analyze certain studies. Analysis have become "standard" over the years because that's the way they have always been done and have been accepted by the FDA. Companies may be nervous about submitting analyses that are non-standard because a reviewer's questions may delay an approval. So a statistician may be less likely to try something new. An advantage of the standard analysis is that production programs can be written to shorten analysis time and insure reliable results. Another part of regulation that affects statisticians is audits. The record keeping, writ-

ing of SOPs, and dealing with auditors, both internally and from the FDA, is not enjoyable for some statisticians.

##### Changes in the Work Environment:

In the past (20 years ago), there were fewer compounds coming out of discovery which allowed development to devote a significant amount of effort in evaluating and optimizing a new compound. Most of the experiments were done using the one-factor-at-a-time approach. During the 1970's, DOE became popular and although the total time for development did not decrease, many scientists saw the benefit of DOE. They were able to gain added information about a compound, solve problems faster, have an organized approach, and were able to answer questions that would arise without additional experimentation. Scientists started to understand the multi-factor approach, to use multiple stage experiments and even began to apply some response surface techniques.

In the 90's, discovery has found ways to screen compounds at a much higher rate, which results in more compounds going into early development. Each of these compounds needs to have assay methods and formulas developed and animal studies performed. These and other activities require more drug substance, so improved drug synthesis is needed. This has put tremendous strain on the development groups. At the same time, companies have become very competitive in getting these new compounds developed and into the market quickly. So the emphasis is on shortening timelines, becoming more efficient, and identifying the "losers." Everyone is expected to do more with less. Scientists do not have time to learn as much about a compound as in the past. Instead of optimizing a process, a scientist may use his best educated guess. If satisfactory results are obtained, the compound moves on to the next step and the scientist moves on to the next project.

This approach has significantly reduced the number of statistically designed experiments as well as the interaction between scientist and statistician. Another change is the increase in out sourced studies, which affects the ability of statisticians to get involved with the development of compounds. Since the work is offsite, statisticians are less likely to get involved with problems that arise. The statistician's role may become more like that of a reviewer. The non-clinical statistician needs to find ways to adapt to these changes.

##### Project Type/Statisticians Interests:

As mentioned earlier, nonclinical statisticians work with many different functional areas. The types of projects that these areas generate are diverse. Based on a statistician's interest, one type of project may be more desirable than another. The combination of project type and interest affects how a statistician will respond to the survey questions. Projects generated by scientists in the functional groups can be of two types. The first project type includes projects that have always been done a certain way and there is no real desire to change how the analysis is performed.

In this same category are "production" type analyses. These are the routine in-house analyses that don't require any new approaches. There may be computer programs that are just rerun with minor modifications. There may be little interaction between scientist and statistician. The second type of project involves solving a new problem or finding a different approach to an old problem. Some of these problems are fairly well defined but not solved or they may be problems that require much more interaction between statistician and scientist. Statisticians who don't enjoy the consulting aspect of the job may enjoy the well defined problems. For those problems that are not well defined, the statistician is required to have good consulting skills, needs to ask the right questions, determine an appropriate approach, or may need to find out more about the science, etc. There is a third project type that is not generated by the scientist but by the statistician. These "reaching out" type of projects require a statistician with the "pioneer" spirit. The statistician needs to be part salesman, recognizing where statistics can have an impact, determining the need for statistical advice, selling the scientists on the benefit, putting the right tools in place, selling to upper management, etc. These kinds of projects require good people skills. In the past, management usually performed these types of projects, but now statisticians at all levels should be involved in these activities. A statistics group should have a blend of statisticians who enjoy being involved with all three of these project types. Although there will always be a need for statisticians to perform standard analysis and to solve the well defined problems, the demand for statisticians with good consulting and pioneering skills will continue to grow.

### Conclusions

The survey results indicate that training is an important tool for conveying the importance of getting statistical input during the design stage of a product. To have a lasting impact, training should use examples from the application area and include hands-on experiments where appropriate. One-on-one interaction is the best way to get scientists to think like statisticians. Most responders think that statisticians should train on the job rather than have a formal degree in an application area. The most common challenges that statisticians face are becoming a valued team member, dealing with shortened timelines, and getting upper management support.

## Discussion

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My responses to the six survey questions are the following:

1. How can statisticians convey the importance of statistical input at the design stage?

The best way is to get involved in a research or development project as a team member. Almost all projects have meetings. Attend the meetings. Obtain knowledge of the field. Participate and become an active member of the research or development project. As an active team member, contribute statistical input at the design stage.

2. How can statistical concepts be explained without jargon?

Again, I come back to partnering with a scientist as part of the team. The statistician has to understand the scientist's jargon and vice versa. Explain statistical concepts by using examples in the application area.

3. What background should be required for a statistician in an application area?

The statistician should have excellent oral and written communications skills. Also, the statistician should have the personality and patience to work with diverse individuals in a team environment. Knowledge of the scientist's subject matter is very important. Ask the scientist for some textbook and journal references. Attend seminars and staff meetings with the scientists.

4. How much time should be spent on training scientists?

Short courses and seminars are good for introducing general concepts. However, partnering with a scientist gives the opportunity for constant training. Statistical concepts are enforced by the scientist's continuous use in the application area with collaboration from the statistician.

5. How can statisticians get scientists to think like statisticians?

When a scientist and statistician are working closely together on a project (e.g. joint publication), each will develop an understanding of the other's thought processes. One on one interaction is the best way to accomplish the task.

6. What do you feel is the most common challenge for statisticians?

The most common challenge is to become a valued team member. Upper management's responsibility is to create an environment where work is accomplished as a team and not by individuals.

From the answers to the survey question, it is clear that I believe in a very active partnership with research and development. At all levels of the Nonclinical Statistics group, the statistician should participate with the scientists at staff meetings, professional association presentations, and management reviews. Upper management support comes with demonstration of increased efficiency and project success through partnership with statistics.

I agree with Jim Bergum with his description of the factors influencing survey results and his conclusions. I close my discussion by giving a short list of references for Nonclinical Statistics.

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## Discussion

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As Jim stated, the motivation for this survey was to get background information for a panel discussion on the practice of statistics. Jim should be complimented for taking the effort to gather data on the topic rather than just shooting from the hip. As Jim acknowledged, his survey is based on a convenience sample rather than a probability sample. I could quibble with his noncompliance to basic sampling survey principles; however, since the results generally concur with my view of the state of nature, I will pass on challenging Jim on his survey methods. Since Jim did not shoot from the hip, I will exercise that privilege in giving my views on the questions raised.

*Input at the Planning Stage.* In contrast to the practice in clinical trials statistics, the nonclinical statistician does not usually sign off on study protocols. Although I have always been uncomfortable with this situation, there are several practical reasons for this state of affairs. First, in the discovery phase much experimentation is exploratory or screening in nature, not to confirm a prespecified hypothesis. There are also minimal regulatory requirements at this stage. Second, many studies in the preclinical development stage, particularly in the path/tox area, repeatedly use the same long-established study plan, whatever the class of drug being developed. Given that thousands of studies are done each year in discovery and preclinical drug development, statistical manpower is just not available to review each individual study plan. Still, study design is always foremost in our minds and we spend a lot of time and effort promoting good experimental design.

As the survey indicates, we do this by giving training courses to scientists and engineers on experimental design. Other steps that we have taken to promote design of experiments (DOE) include holding symposiums where scien-

tists and engineers share with their colleagues how they have used DOE in their applications. We have also established a DOE advisory group of senior research scientists and engineers and have an active DOE team in our department that meets regularly to plan activities. Also, as the survey indicates, one-on-one interactions between the statistical and research scientists is a vital way of influencing study design. As Fisher noted, the best time to plan an experiment is when you have just completed the experiment.

*Explaining Statistical Concepts.* The human side of statistical consulting is very important [1]. Clear communication is critical to building a good working relationship with the research scientist. It takes patience and hard work to avoid jargon and explain our concepts but it is very much appreciated by the scientist. Over and over again, we find that the scientists want examples from their application area. Everyday examples can also be used to call attention to the role of chance and variability in interpreting data.

*Background.* I have seen statisticians from a wide range of backgrounds achieve success. I think talent, good statistical training, a strong work ethic, and an ability to communicate are more important than some prescribed background. Having said that, I am concerned that many graduate schools seem to select primarily on mathematical credentials while turning away, or turning off, individuals with a science background.

*Training Scientists.* This is a challenging area. First, with the time pressures we live under, there is little time to develop and teach courses. Also, the research scientist is interested in courses only if they can be kept brief, say, a couple of half days. Still, I think we must give courses in the fundamentals of statistical thinking and experimental design. We find this training is best received when given with a course teaching the scientists how to use statistical software packages. The scientists want such courses and they provide an opportunity to nurture a good relationship between disciplines.

*Statistical Thinking.* I think one-on-one interaction, coupled with an occasional course, is the best way to promote statistical thinking. Our best advocates are scientists who have worked closely with statisticians. Those who have seen the benefits of statistical tools and reasoning in their own research convey that message to their colleagues.

*Challenges for Statisticians.* I concur with Jim that our primary challenges are becoming valued team members, dealing with shortened timelines, and getting upper management support. Also, I have never seen so many rapid and exciting developments and opportunities in drug discovery as we see now with new technologies such as high throughput screening and human genetics. Our world is clearly changing, and we must meet these new challenges. In addition to not missing these new opportunities in drug discovery, we must continue our strong participation in preclinical drug development. Yes, we do live in interesting times.

Jim's survey covered many important bases. He appropriately focused the survey on what we are doing for the research scientists. Nonetheless, I would have liked to have seen a question directed toward the statisticians' quality of life. For example, how pleased are we with the contributions we are able to make to the research process? Do we have time to do a quality job?

In closing, I really appreciate Jim following up on his survey and panel discussion with this written report. In addition, to giving information to us in the field as to what our colleagues are doing and thinking, Jim's paper is a good document to share with those who are considering jobs in nonclinical statistics.

References:[1] Boen, J. R. and Zahn, D.A. (1994). *The Human Side of Statistical Consulting*, Lifetime Learning Publications, Wadsworth, Inc., Belmont, California.

## Discussion

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I appreciate the opportunity to share my thoughts on the survey questions and Jim's observations.

*Conveying the Importance of the Statistical Input at the Design Stage of the Project.* As we all know, this is the heart of the matter in nonclinical statistical work, and arguably has more impact on the projects overall success than any other factor. Perhaps the best solution is a combination of general training on DOE for scientists, complemented by customized training in the application area.

The general training on DOE should be carried out by statisticians with experience in the application area of the scientists, and should make use of published examples, both good and bad. Used with permission of the scientists, examples from within the company can be extremely effective, and make the training much more relevant.

In a project team environment, roles in general are reasonably well defined, for both design and implementation. In most cases, the project statistician has the opportunity and the responsibility to contribute to the design of the experiment.

In a one-on-one environment or in small collaborative teams where the formal rules and clearly defined responsibilities that exist in the project team environment are absent, several factors play a role in determining a statistician's opportunities for providing input at the design stage. Her knowledge of the application area, her perceived commitment to the upcoming work, and her availability are all factors.

And then there's location, location, location. In my experience, locating statisticians with the scientists greatly increases opportunities for continuous interaction and strengthens involvement in their work.

*Explaining Statistical Concepts without Jargon.* This is certainly one of the most challenging tasks facing statisticians. While some scientists have very good knowledge and understanding of statistics in their fields of expertise, others have limited knowledge and understanding of basic statistics and concepts. There are also scientists who labor under mistaken or incorrect concepts about the basics of statistics. Avoiding jargon while explaining statistical concepts to scientists who belong to any of these groups takes work.

First, the statistician must have the necessary knowledge and a clear understanding of the concepts as they apply to particular field of knowledge. A simple self-test for this is whether she can explain the concepts from different angles in her own words, and point out what these concepts do not mean. Second, she needs to assess the statistical knowledge of her various audiences. Third, she needs to use examples from the scientists' field in which these concepts are implemented. She can show where these examples are explained and implemented correctly and examples where concepts are incorrectly implemented and explained.

If the statistician is not an experienced presenter or if establishing credibility with this particular scientist is considered to be very important, then it is good to have a rehearsal with more experienced statisticians. Even better, the statistician could rehearse with scientists with whom she has developed a high level of credibility and a good working relationship.

*Required Background for a Statistician in an Application Area.* To be successful in any mode of collaborative work with scientists, knowledge of the application area is very important. The knowledge of the application area is in general acquired as a part of the on-the-job training. Responsibility for on the job training falls on the shoulders of both the statistician and her departmental supervisor. Her supervisor should help her identify resources for training, both internally and externally, and insure that financial resources, such as fees for courses, are made available.

The statistician is responsible for the effective use of training resources. She must make it her business to become knowledgeable and to keep up with developments in the application area and in her field on an ongoing basis. She is also responsible for developing other necessary and important skills for collaborative and consulting work, such as written and oral communication skills, presentation and listening skills, and conflict resolution skills. These critical skills will not only help her to be successful in her work life, it will help her grow professionally and personally as well.

*Training Scientists.* Depending on their field and degree, many scientists have taken one or more statistics classes and thus have been exposed to at least the basic statistical concepts during their formal university education. As a part of the statistical and quantitative literacy program, a one-to-three day, well organized and coordinated General Statistical Concepts and Foundation courses should be made available to scientists by their companies.

Scientists who were not exposed to statistical concepts, or who were exposed to them very early in their education, should be strongly encouraged (or perhaps required) by their employers to take the sequence of General Statistical Concepts and Foundation courses. Furthermore, any scientist who feels the need to attend these courses to refresh basic statistical knowledge should also be encouraged to attend.

Each part or module of these courses can be prepared and taught by the statisticians who most likely will work with the scientists who are attending the courses. The courses could be made more attractive to the scientists by enlisting scientists who have thorough knowledge and experience to prepare and teach modules of the courses. Occasionally, statisticians and scientists from outside the company can be invited to prepare and teach particular modules, bringing new perspectives and ideas to the courses.

Application area specific training is request-based and it is in general continuous in nature. As such, it is carried out either in the project team environment or on a one-on-one basis. This training is generally informal.

In the project team environment, decisions concerning the scope, timing, level and duration of the training are made by the project team leader. In one-on-one collaborative projects, the project scientist determines the scope, level, timing, and duration of the training.

*Getting Scientists to Think Like Statisticians.* An effective and successful collaboration between statisticians and scientists does not require scientists to think like statisticians when they are working together on a project. Based on my own experience and observations, I consider the following points as determinants of effective and successful collaborative work with scientists, in both one-on-one and project team environments.

- Reasonable understanding of each other's field so that meaningful discussion and questioning can take place to clearly define the problem facing them and to explore solutions for it.
- Genuine openness in the dialog and in questioning of each other while they are searching for solutions.
- Integrity and professional courtesy in dealing with each other's viewpoints, especially when parties are in strong disagreement with each other.
- Acknowledgement of the contribution made by the other colleague — openly, appropriately, and at times and places where it counts. That is, sharing the success as well as failure.

*Most Common Challenge for Statisticians.* Pharmaceutical companies have been accumulating enormous amounts of data and information in many fields of nonclinical and clinical research and development. Few, if any, pharmaceutical companies have converted these data and information into knowledge and made it available to their top management for use in the identification and definition of strategic initiatives or for use by R&D personnel in their drug development activities. Integrating available information and creating knowledge are the high impact projects. I think there is

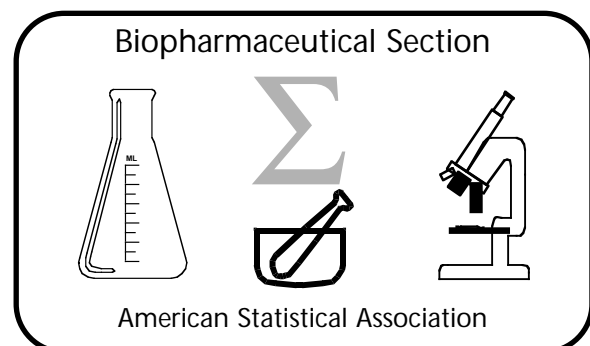
great opportunity for statisticians to take the lead and play a key role in the creation of knowledge and knowledge bases.

I would like to comment on a point Jim made under the Project Type/ Statistician's Interest subheading when he was discussing the factors that might have influenced the survey results.

I believe that, whether we as statisticians like it or not, there is no meaningful work in any industry, and especially in the pharmaceutical industry today, that does not require a statistician to be good at the consulting aspect of the job — and to like it. I am talking about work that leads to professional and personal growth, promotion, and fulfillment — and year in, year out routine production work is never going to result in any of these benefits. Yes, quite a lot of routine and production-type statistical analysis are carried out in the nonclinical area. However, many of these analysis are done by application area scientists. These scientists are quite knowledgeable and competent to carry out these analysis; they know when to seek help, not only in design and analysis but also in the interpretation of the results, and the statisticians do the rest.

In a statistics unit, each statistician's workload should include a mix of projects: some routine projects, for decompression (few people can work on highly interactive, path-breaking projects indefinitely); some consulting projects; and some of what Jim calls "reaching out" projects. The percent of time allocated for each type of work can vary from statistician to statistician, depending on their knowledge, experience, and skills, as well as on the strategic focus of the company.

While one may appreciate the motivating factors, it would be a disservice to both the statistician and the corporation to hire statisticians dedicated solely to routine and production-type work. This practice limits the growth potential of incoming statisticians and creates an environment for the development of a class system within the group. Likewise, for existing statisticians who do not like consulting work there is a tendency to gravitate toward doing mostly routine analysis work. It is a mistake for the manager to allow this to happen. Furthermore, since this kind of routine work is often targeted for automating or outsourcing, the jobs of these statisticians may be in jeopardy as corporations pursue more efficient ways of operating. As Jim correctly stated, a strong statistics group "should have a blend of statisticians who enjoy being involved with all three project types."



## Section News

### Letter from the Chair

Steven Snapinn

As you may have noticed in the last issue of the Biopharmaceutical Report, the Biopharmaceutical Section recently crossed a major milestone: Just in time for the new millennium, the section now has over 2000 members! Based on a recent accounting from the ASA office, our section has 2044 members, second only to the Statistical Computing section (2370), and just ahead of Biometrics (1943) and Statistical Graphics (1898). The increase in our membership is due to a number of factors, not the least of which is the outstanding and tireless effort of the chair of the Membership Committee, Phil Pichotta.

I like to think that another factor contributing to this increase is the great value that you get from membership in the Section. I'm sure you'd all agree that, even with the recent increase in dues from \$5 to \$7 per year, membership in the Biopharmaceutical section is a bargain. For example, those of you who attended the sections mixer in Baltimore might be interested to know that you consumed the equivalent of one year's dues with your first four mini-egg rolls! (I have to admit that I've never had a bigger sticker shock than when I saw the price list for hosting a mixer. As the father of two teenage girls, college costs are no longer my biggest financial concern – catering a wedding at a hotel will dwarf even an Ivy League education.) As another example, your annual dues, which include a subscription to the Biopharmaceutical Report, cost less than a single issue of the Journal of the American Statistical Association. Now, be honest, where do you get more useful information, from JASA or the Biopharmaceutical Report?

With so many new members, I thought it might be a good idea to review the objectives of the Biopharmaceutical Section:

- To aid the American Statistical Association and its sections in the effort to create, promote, and stimulate interest in the advancement of the field of statistics.
- To encourage the appropriate and valid use of statistical methods in the biopharmaceutical industry.
- To encourage the development of new statistical methods for application to health-related problems.
- To cooperate with government, academia, business, and industry in resolving important scientific issues which affect the health sciences.
- To develop standards of design, evaluation, and reporting of biochemical, biological, human, and animal health experimentation.

- To promote the application of statistical methods to biopharmaceutical problems as an interesting and rewarding field of study.
- 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.

That's an ambitious set of objectives, and we're doing our best to try to meet them. One thing that's become clear to me during my tenure as Chair-elect and Chair is that we have an extremely well-functioning Executive Committee and an active and committed membership. My role as Chair has been a piece of cake. The Executive Committee is a well-oiled machine, thanks in large part to the work of the last few Chairs, including Ken Koury, Bob Davis and Gary Neidert. And whenever there's any work to be done, there's never a shortage of volunteers. If anything we have the opposite problem: There are more members who would like to contribute their time to the Section than there are tasks. It's really a pleasure to work in an environment like this. Rather than thank everyone individually at this time (I'll save that for a later column), I invite all of you to have a look at the rogue's gallery in the section's web site (<http://www.best.com/~asabp/>; photos courtesy of Sally Greenberg).

The Executive Committee supplies services to its members by, for example, organizing sessions at ENAR and the Joint Statistical Meetings, cosponsoring other conferences and workshops, providing publications like the Biopharmaceutical Report and the Proceedings of the Biopharmaceutical Section, and encouraging excellence through awards for best contributed paper presentations and best student papers. What we'd like in return is your active participation in the Section. Hopefully, your role will include sending us ideas on how the Section can better serve its membership, attending conferences and sessions sponsored by the Section whenever possible, and contributing to the electronic discussion list. Honestly, the discussion list has so far been a bit of a disappointment. A large fraction of the traffic is currently made up of messages from those of us (myself included!) who have inadvertently replied to the list rather than to an individual, and automatic out-of-office replies. The list has great potential but is underutilized.

So, to conclude, like the Dow Jones average I hope our membership continues to grow. It took the Dow 13 years to climb from 2000 to 10000; let's see if we can do it even faster!

# Biopharmaceutical Section Electronic Mailing List

**Sally Greenberg**

*Secretary/Treasurer and Mailing List Moderator*

In November, 1996, the Biopharmaceutical Section began sponsoring an unmoderated electronic discussion list for exclusive use by members of the ASA Biopharmaceutical Section: [asabiopharm@lists.best.com](mailto:asabiopharm@lists.best.com)

Only ASA Biopharmaceutical Section members who are subscribed to this list can post to and receive mail from the list. All ASA Biopharmaceutical Section members are welcome (and encouraged!) to join. The messages posted to this list represent the views of the authors and have no explicit or implicit endorsement by the Biopharmaceutical Section of ASA.

The primary purpose of this list is to foster communication among, and disseminate information to, the members of the ASA Biopharmaceutical Section. It can also be used as a forum for identifying topics for future technical sessions and workshops. As such, messages on the following topics are actively encouraged:

- Discussion of issues which are relevant to section members (e.g., implementation of regulatory requirements and biopharmaceutical statistical methodology)
- Announcements of relevant meetings & workshops (regardless of the sponsoring group)
- Occasional postings of relevant job advertisements also fall within the scope of the list. However, postings which advertise products or services are expressly prohibited.

The Biopharmaceutical Section Executive Committee would very much like to encourage all section members to join the list and initiate/join in discussion. Ultimately, the list is only as useful as the membership makes it. Several interesting discussions have occurred, but we'd certainly welcome more!

Confidentiality of list membership is maintained, with the names and email addresses of

subscribers being made available only to the ASA Biopharmaceutical Section Executive Committee.

To subscribe to the digest version of the list, Biopharmaceutical Section members should send an email message as follows:

Address the message to: [asabiopharm-request@lists.best.com](mailto:asabiopharm-request@lists.best.com)

The body of the message should contain the two lines:

```
# your name (as listed in the ASA
  directory)
  subscribe
```

Digests (containing all messages since the previous digest) will be generated approximately once a day (assuming that one or more messages have been posted).

To subscribe to the individual message version of the list, rather than to the digest version, Section members should instead send an email message as follows:

Address the message to:  
[asabiopharmrequest@lists.best.com](mailto:asabiopharmrequest@lists.best.com)  
The body of the message should contain the two lines:

```
# your name (as listed in the ASA
  directory)
  subsingle
```

Currently there are few enough postings on the list that all list members receive individual messages. However, if the list becomes a lot more active, list members will receive individual messages or digests according to their preference when they subscribed.

Section members who experience any difficulties with subscribing or posting should email Sally Greenberg ([asabp@best.com](mailto:asabp@best.com)), who is the List Owner/Moderator for [asabiopharm](mailto:asabiopharm).

## Biopharmaceutical Section Web Site

**Kalyan Ghosh**

*Liaison to Applied Statistics Conference and Webmaster*

The Biopharmaceutical Section maintains a Web site at the URL [www.best.com/~asabp/](http://www.best.com/~asabp/). (It can also be accessed through the ASA Web site at [www.amstat.org](http://www.amstat.org)). Although this is a relatively new URL for the sections Web site, the section has been present on the net for almost 3 years. The site is a repository for section announcements, activities and resources. If you want to post anything on this site that may be of interest to the section members, please send it (in any pc-readable format) to [kalyan\\_ghosh@merck.com](mailto:kalyan_ghosh@merck.com). We welcome any suggestion you may have for improving the Web site. Also, if you are willing to volunteer to work on the Web site or on any other section activity please drop a line at the same email address.

These two documents are reprinted from the May 1999 Amstat News Issue

## FDA/Industry Workshop *Statistical Issues for the New Millennium*

The fourth annual FDA/Industry Statistical Workshop will be held September 30 - October 1 1999 in Arlington Virginia at the Hyatt Regency Crystal City.

Ralph Harkins (Quintiles) and Nancy Smith (FDA) will co-chair the workshop. Program committee for the workshop included Charles Anello (FDA), Harry Bushar (FDA), Greg Campbell (FDA), Ralph Harkins (Quintiles), Sandy Heft (Schering Plough), Henry Hsu (FDA), Lukas Makris (BioCor), Anna Nevius (FDA), Bob O'Neill (FDA), Tony Segretti (Glaxo Wellcome), Robert Small (Pfizer), Nancy Smith (FDA) and Ji Zhang (Merck & Co).

Registration form in PDF format is available at the Biopharmaceutical Section Web page (<http://www.bestcom/~asabp/fda99.htm>). For further information contact ASA Meetings Department, 1429 Duke Street, Alexandria, VA 22314, (phone) 703-684-1221 ext. 148, (fax) 703-684-8069.

### Preliminary Program

#### Thursday, September 30, 1999

- 8:00 a.m.–8:30 a.m.** Continental Breakfast
- 8:30 a.m.–8:45 a.m.** Welcome
- 8:45 a.m.–10:15 a.m.** Regulatory Roundtable—FDAMA and Beyond
- Organizer/Moderator: N. Smith, Food and Drug Administration
  - Statistical Leadership from several Centers of the FDA will discuss the role of statistics in our changing regulatory environment
- 10:15 a.m.– 10:45 a.m.** Morning Break
- 10:45 a.m.–12:15 p.m.** Interim Analysis and Data Safety Monitoring Boards
- Organizers: R. Harkins, Quintiles; M. Huque, Food and Drug Administration
  - Chair: R. Harkins, Quintiles
  - Speaker: "Interim Analysis and Data Monitoring," G. Chi, Food and Drug Administration
  - Speaker: "DSMB, Problems and Solutions" S. Snapinn, Merck & Co.
  - Speaker: "Interim Analysis," J. Lachin, George Washington U
- 12:15 p.m.–1:30 p.m.** Lunch (on your own)
- 1:30 p.m.–3:00 p.m.** Meta Analysis Applied to Non-Inferiority Trials
- Organizer: H. Hsu, Food and Drug Administration
  - Chair: A. Lachenbruch, Food and Drug Administration
  - Speaker: "Some Approaches for Meta-Analysis in Non-Inferiority Trials," A. Gould, Merck
  - Speaker: "Issues on Meta-Analysis of Sepsis Trials," J. Wittes, Statistics-Collaborate
  - Speaker: "Experience on Meta-Analysis of Cough-Cold Preparation," R. D'Agostino, Sr., Boston U
  - Discussant: C. Anello, Food and Drug Administration
- 3:00 p.m.–3:30 p.m.** Afternoon Break
- 3:30 p.m.–5:00 p.m.** Multiple locations, inference space, mixed models, and their impact on design and analysis of experiments
- Organizers: A. Nevius and J. Derr, Food and Drug Administration
  - Chair: A. Nevius, Food and Drug Administration
  - Speaker: "An Academic Statistician's Perspective," W. Stroup, U of Nebraska
  - Speaker: "An Industry Statistician's Perspective," A. Dayton, Pfizer Animal Health
  - Speaker: "An FDA Statistician's Perspective," J. Gilbert, Food and Drug Administration
- 5:00 p.m.–6:30 p.m.** Reception (Cash Bar)

#### Friday, October 1, 1999

- 8:30 a.m.–10:00 a.m.** Three Simultaneous Sessions
- Session 1: Use and Misuse of Covariance Analysis in Clinical Trials**
- Organizers: K. Kazempour, Amarex; R. Harkins, Quintiles
  - Chair: K. Kazempour, Amarex
  - Speaker: "We should Kill and Deal with the Known Covariates in Design Stage," S. Hedayat, U of Chicago
  - Speaker: "Model-searching is dangerous but pre-specifying is robust," T. Permutt, Food and Drug Administration
  - Speaker: "Analysis of Covariance and Surrogate Marker," A. Balch, Searle Research and Development
- Session 2: Statistical Issues in Diagnostic Medical Products**
- Organizers: H. Bushar, Food and Drug Administration; L. Makris, BioCor
  - Chair: J. Castellana, Berlex Laboratories

- Speaker: D. Hawkins, U of Minnesota
  - Speaker: "Measures of Agreement: Recent Advances and Future Directions," M. Donovan, Covance
  - Speaker: "Discrepancy Resolution," K. Meier, Food and Drug Administration
- Session 3: Statistical and Interpretive Issues in Health Related Quality of Life Data**
- Organizers: J. Zhang, Merck Research Laboratories; C. Gnecco, Food and Drug Administration
  - Chair: J. Zhang, Merck Research Laboratories
  - Speaker: "Interpretation of changes and between group differences in HRQL," N. Santanello, Merck Research Laboratories
  - Speaker: "An FDA Review Perspective on Statistical Design and Analytic Aspects for Studies with HRQL Endpoints," C. Gnecco, Food and Drug Administration
  - Speaker: "Biostatistical challenges created by quality of life research," I. Barofsky, Johns Hopkins U School of Medicine
- 10:00 a.m.–10:30 a.m.** Morning Break
- 10:30 a.m.–12 noon** Three Simultaneous Sessions
- Session 1: Some Approaches to Postmarketing Surveillance Safety Assessment**
- Organizers: C. Anello, Food and Drug Administration; R. O'Neill, Food and Drug Administration
  - Chair: C. Anello, Food and Drug Administration
  - Speaker: "Special Issues in Monitoring Vaccine Safety," S. Ellenberg, Food and Drug Administration
  - Speaker: "Evaluating Methodologies for Analysis of ADRs in Marketed Products," S. McDermott, Glaxo Wellcome
  - Speaker: "Assessing Gender effects from a large Spontaneous Reporting Data Base," A. Szarfman, Food and Drug Administration
  - Discussant: R. O'Neill, Food and Drug Administration
- Session 2: Perspectives in the Use of Bayesian Statistics in Clinical Trials**
- Organizers: G. Campbell, Food and Drug Administration; K. Ghosh, Merck
  - Speaker: TBA
  - Speaker: A. Grieve, Pfizer
  - Speaker: T. Irony, Food and Drug Administration
- Session 3: The Design and Analysis of Studies to Assess the Effect of Inhaled Steroids on Growth**
- Organizers: A. Segretti, Glaxo Wellcome, S. Wilson, Food and Drug Administration
  - Session Chair: R. Liddle, Glaxo Wellcome
  - Speaker: "Overview of Topic," Speaker TBA
  - Speaker: "A Pharmaceutical Industry Perspective," S. Duke, Glaxo Wellcome,
  - Speaker: "An FDA Perspective," B. Elashoff, Food and Drug Administration
- 12:00 p.m.–1:15 p.m.** Lunch (on your own)
- 1:15 p.m.–2:45 p.m.** Issues in the Analysis of Data with Missing Values
- Organizers: R. Small, Pfizer; E. Nevius, Food and Drug Administration
  - Chair: R. Small, Pfizer
  - Speaker: "Testing for treatment differences with dropouts present in clinical trials—a 'pattern but not mix' approach," W. J. Shih, Merck & Co.
  - Speaker: "Missing Data—Does it matter?" G. Tudor and V. Hasselblad, Duke Clinical Research Institute
  - Speaker: TBA, Food and Drug Administration
- 2:45 p.m.–3:00 p.m.** Closing and Evaluations

**Let's Hear from You!**

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