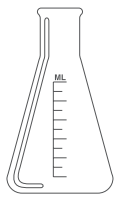


Biopharmaceutical Section



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Chair: *Stacy Lindborg*

Editors: *Richard Caplan, Philip Pichotta*

Note from the Editors

Since 1999 Demissie Alemayehu has been an editor of the *Biopharmaceutical Report* for 6 years involving 13 issues. We want to thank him for his efforts that he has done to support communication within the Biopharmaceutical Section and hope to continue to provide articles of interest to our membership. This issue has 2 articles representing different views from statisticians working with biomarkers in clinical development. Our next issue will have an article about development of a biomarker. Many of us have not had the experience of working with biomarkers, and we hope that these articles will some background on biomarkers and their use in drug development. This issue also contains information about past and upcoming activities in the Biopharmaceutical Section. Finally we hope to have all the issues of the *Biopharmaceutical Report* available on the Section website soon. Eventually, we hope to have an index of articles and authors to help search for articles. ■

Letter from the Chair

Stacy Lindborg

It is my pleasure to address you as one of the many volunteers of the largest section of the ASA. While it is early in the year, the Executive Committee has many exciting things that we plan get under way in 2006. It is our intent that we will continue to evolve and provide benefits to our body of members which will allow us to grow and accomplish even more.

We find ourselves with a healthy budget in 2006 yet again (thanks to the hard work of Corporate Sponsorship Committee chair Jim Colaianne and his committee Russ Helms, Kay Larholt and Alka Preston). The Executive Committee continues to ponder a question posed by past-chair Leonard Oppenheimer: What should the section be doing to further support students, promote the use of statistical science to benefit society, to enhance our continuing education and professional meeting opportunities, to assist statisticians in countries or situations with insufficient resources? Based on the first Executive Committee meeting of 2006, we will have some exciting ideas to share before the end of the year. Stay tuned!

It is amazing how quickly one year speeds by. However, in this year as your chair I hope to have impact on the section in a variety of ways:

✓ Continue to diversify representation on the Executive Committee to better serve our broad membership. Dating back to the Summer of 2001, Jeff Meeker reflected on the changing face of the leadership Biopharmaceutical Section. In these days he referred to an image of an 'old boy's club' that they were trying to shake. Well, we're proud to present numbers of >30% female membership in the ranks of leadership. The current challenge at hand relates to diversity of research. According to Section 2 of our charter our section states that "the special interest of the Biopharmaceutical section is the application of statistics in the development and use of therapeutic drugs, biologics and devices in humans and animal". While I believe our activities and influence on the scientific programs at ENAR and JSM have been friendly to the breadth of this statement, we can always do better. In an attempt to bring more acute awareness to the breadth of our mission in our leadership group, I have used my two Executive Committee appointments to welcome Andrew Mugglin (devices), Mark Chang (biologics) to the group. We have also begun discussions recently

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with a group of individuals interested in forming an Animal Health special interest group. There will be a meeting at the Biopharmaceutical sponsored meeting Midwest Biopharmaceutical Statistics Workshop (MBSW) in May.

- ✓ Continue the effort to update our manual of operations. Many of our appointed or volunteer roles do not have established length of service in our manual of operations. As a result, some volunteers end up in positions with tenure! In an effort to be fair to those volunteers who graciously give of their time and to create more opportunities for others to get involved, the Executive committee has reviewed a list of positions and proposed appropriate lengths of service (with the option for renewal at the end of the term, of course!). We will be updating the operations manual with much greater detail as the year progresses. While this manual is primarily a resource for individuals currently serving in roles, it should also be viewed as a resource to our entire membership to understand roles better for potential future interest. If you have interest in getting involved in specific roles or questions about ways you can get involved, I encourage you to attend our annual Business meeting at JSM and get to know members of the current Executive Committee. An email will be sent to the entire membership in advance of the JSM with details of the meeting.

Two individuals whom I especially want to thank for outstanding years of service include **Nandita Biswas** (Webmaster) and **Demissie Alemayehu** (Biopharmaceutical Report editor). Nandita has served our section countless years by efficiently maintaining the website. As she departs this role, we welcome Daniel Christen to the group as webmaster. Demissie's tenure with the Biopharmaceutical Report dates back to at least 1999! During this period he has served as publication officer, worked as Biopharmaceutical Report co-editor along side colleagues, led the charge as Biopharm Report Editor, and more than once went above and beyond and continued his role as Editor when others were unable to keep their commitment. I would love to honor him with the title of Biopharmaceutical Editor Emeritus, but I'm afraid he'll feel that we truly aren't going to let him step down. Many thanks Demissie for your dedicated service and impact on our section. While these are big shoes to fill, I am thrilled to welcome Richard Caplan and Philip Pichotta, both very capable gentlemen to the roles of Editor and to Editor-elect, respectively.

By the time you receive this report I hope you have cast your ballot for future elected leaders to the Biopharmaceutical section and ASA more broadly. Some of you might have noticed that secretary was missing from the Ballot. In 2003 the Biopharmaceutical Section amended our charter

to divide the roles of Treasurer/Secretary into 2 separate 3-year terms. Mani Lakshminarayanan was appointed to serve as treasurer from 2006 – 2007 and our intent was to elect a Secretary in 2006, thereby staggering the roles. However there was some confusion with the ASA office and the names submitted by the Nomination committee were left off the ballot. Margaret Minkwitz graciously volunteered to extend her term as secretary and Devon Mehrotra will be appointed to serve as secretary for 2007-2008. I have no doubt the Nomination Chair for 2006 (Len Oppenheimer) will make sure we get on track with elections for both roles.

We intend to conduct another membership survey in 2006. However, the Executive Committee would welcome any comments that would help us understand how we could serve the section better. Hope to see many of you at JSM! ■

Midwest Biopharmaceutical Statistics Workshop update

Brian L. Wiens

2006 MBSW Chair

Record attendance and an exceptionally well-received program highlighted the 2006 Midwest Biopharmaceutical Statistics Workshop May 22-24 in Muncie, Indiana. The Workshop, commonly known as "The Muncie Meeting," was held for the 29th consecutive year on the campus of Ball State University in Muncie, Indiana. The Workshop is co-sponsored by the Biopharmaceutical Section of the ASA.

Tremendous appreciation is due to the organizing committee. Technical sessions were spearheaded by Amit Bhattacharyya (GlaxoSmithKline), Devan Mehrotra (Merck) and Kjell Johnson (Pfizer) for the oral sessions and by Caroline Lee (Pfizer) and Kim Perry (Innovative Analytics) for the poster session. Administrative functions were led by registrars Tammy Forrester and Simin Baygani (Lilly), publicity chair Melvin Munsaka (Takeda) and treasurer Jackie Reisner (Pfizer). Charlie Sampson and Mir Ali provided mentoring and guidance, as they have for all 29 years of the Workshop. Other features of the 29th MBSW included a short course presented by Brenda Gillespie of the University of Michigan, a plenary address presented by Raymond Carroll of Texas A&M University and a banquet talk by Bruce Rodda of Strategic Statistical Consulting LLC and the University of Texas. The Charlie Sampson Award for best student poster was awarded to Melissa Spann of Baylor University.

Planning has already begun for the 30th annual meeting, scheduled for May 21-23, 2007. Workshop chair-elect Mani Lakshminarayanan (Mani.Lakshminarayanan@Pfizer.com) has formed a committee to organize this meeting. Please check the website (www.mbswonline.com) for program announcements and registration, which will be available in early 2007. Organizers of the first Workshop and chairs of the subsequent 28 Workshops are strongly encouraged to attend to help celebrate the milestone. ■

Biomarkers in Drug Development: *Friend or Foe?*

Kevin Carroll

AstraZeneca Pharmaceuticals

Introduction

With the advent of proteomic, genomic and genetic technologies, the era of personalised medicine is dawning, or at least that appears to be the view coalescing across industry, academia and regulatory health authorities alike. In addition, efforts to gain a more in depth biologic understanding of disease, particularly in oncology, is simultaneously leading to the identification of a whole host of biomarkers that reflect underlying biologic processes and the aetiology of disease. But what exactly is a 'biomarker'? For the purposes of this article, the terms 'biomarker', 'surrogate endpoint' and 'clinical endpoint' will be defined as per Gruttola [1]:

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Clinical Endpoint (or Outcome): A characteristic or variable that reflects how a patient feels or functions, or how long a patient survives.

Surrogate Endpoint: A biomarker intended to substitute for a clinical endpoint.

Despite clear definitions in the literature, it is not uncommon in practise for biomarkers and surrogate endpoints to be confused, with the terms often (and incorrectly) used interchangeably. However, the distinction between the two is particularly important in drug development and more will be said about this later.

As evidenced by FDA's Critical Path Initiative and EMEA's Pipeline Program, regulatory authorities are looking at the drug development process, hoping to see and encourage the prospective identification of patients who will gain most benefit from new medicines while reducing ever-lengthening development times.

With an increased focus on biomarkers comes high expectations. Herceptin (trastuzumab) and Gleevec (imatinib mesylate) are two often-cited biomarker led development successes which others are encouraged to emulate. For such developments, there is a general belief pivotal trials will be smaller in size (since effect sizes will be larger), less costly and more secure in terms carrying a lesser risk of failure. The benefit:risk ratio will be clearer and reimbursement arguments strengthened by virtue of a narrower indication and a larger treatment effect. The public is looking for the 'right drug, right patient, right time' and biomarkers seem to offer this promise.

But all is not rosy in the garden.

Biomarkers are too often and too quickly labelled as surrogate endpoints for clinical outcome without proper qualification, which can falsely raise expectations. Also, care needs to be taken to avoid the risk of missed opportunities in phase II trials designed to examine only biomarker 'positive' patients on the assumption of no possible chance of therapeutic efficacy in 'negative' patients. Further, care

needs to be taken with early, apparently promising data showing separation in clinical outcomes between biomarker 'positive' and 'negative' patients treated with a new drug; since the observed difference might not in fact be due to the new drug. Over enthusiasm with such data will increase chance of failing in Phase III. And, finally, the widespread belief that biomarker led developments will, in all cases, be cheaper and less risky is not necessarily true.

The remainder of this article is therefore structured as follows: in Section 2, the role of biomarkers as a part of a patient selection strategy is discussed including the issue of prognostic versus predictive biomarkers and issues in phase II and phase III trial design. Section 3 then briefly examines the use of biomarkers as endpoints in the drug approval process, examining what might be needed to elevate a biomarker to the status of surrogate endpoint and reflecting on the sponsors versus the regulators risk. Section 4 closes the article with a brief summary of the main points discussed.

2. Biomarkers to Select Patients More Likely to Benefit from Drug

A chief and increasing use of biomarkers in drug development is to select patients thought more likely to benefit from a new drug. This is nothing new *per se* since all approved therapies are selective to a lesser or greater extent by virtue of their indication. Rather, biomarkers offer the opportunity for a more sophisticated and refined selection of patients on the basis of disease or target biology. It is important to note that the aim is to select patients more likely to benefit from drug; the aim is not, as is commonly perceived, to identify 'responders' (and therefore exclude 'non responders') to drug. Such absolute dichotomisation rarely occurs in nature because, in many instances, underlying biology is a continuum. Prostate specific antigen (PSA) level in prostate cancer, or epidermal growth factor receptor (EGFR) protein expression level in NSCLC or even PANSS score in depression or NIHSS score in stroke are markers and scales that measure and reflect a continuum of disease status and, consequently, there is no magic cut point that separates patients into 'responders' and 'non-responders'. It is easy to see that over simplification of biomarkers in this fashion could result an increased risk of both Type I and Type II errors depending on the stage of development. What we are actually looking to do statistically with a biomarker is to ascertain if the apparent variability in patient response to treatment—or more precisely variability in the treatment effect, drug relative to control,—is likely to be dictated on the average by the biomarker.

2.1 Prognostic versus Predictive Biomarkers

Before discussing trial design issues it is important to emphasise the crucial distinction between prognostic and predictive biomarkers.

Prognostic markers tell you something about clinical outcome independent of therapeutic intervention. An example of a biomarker that was thought to be predictive but was found to be more prognostic might be EGFR receptor mutations in non-small cell lung cancer (NSCLC). Initially data emerged that, in Western patients receiving EGFR inhibitors, clinical outcomes were better in patients with a mutation than in patients without a mutation [2-3]. Subsequently, however, further data emerged in Western patients treated with chemotherapy, which showed that clinical outcomes were better in those with a mutation relative to those without a mutation [4]. So it would seem that having the mutation is a good thing per se, irrespective of therapeutic intervention, meaning that mutations are probably prognostic for outcome in Western patients.

While prognostic biomarkers may have utility in patient enrichment strategies, predictive biomarkers are arguably more important to successful drug development. A predictive biomarker tells you that the effect of a new drug relative to control is related to the biomarker. Examples might be high EGFR gene copy number in NSCLC, which is predictive for the effect of EGFR inhibitors like gefitinib and erlotinib relative to control and high her-2 gene copy number in advanced breast cancer, which is predictive for the effect of trastuzumab.

If a predictive biomarker can be found early in the development process for a given drug, then this may well provide a sensible and secure direction for further development. The challenge is how do we do this? What early work is needed and how should we design phase II trials to help us understand whether a biomarker is likely to be predictive as opposed to prognostic and so provide data and information to help guide further development?

2.2 Some Design Issues in Phase II and Phase III

Where a new drug is not first in class, it is likely that the path for the use of a biomarker as a selection tool will already have been established. However, for a new drug with a novel mechanism of action, the situation is likely to be different. While pre-clinical and translational science work may shed light on the biology of the disease and therapeutic target and thus, in doing so, may further suggest a biomarker that might identify patients more likely to benefit from drug, this body of work is only ever hypothesis generating – it does not prove that a given biomarker based selection strategy will be successful. What is needed is a well designed phase II trial(s) to examine the biomarker hypothesis and, in doing so, to guide the shape and direction of large scale phase III trials.

Phase II designs can be complex but, broadly speaking, options range from trials where all patients are treated with the new drug and outcomes in biomarker 'positive' patients are compared to outcomes in biomarker 'negative' patients – these are poor, relatively uninformative non-

randomised designs—to trials including only biomarker 'positive' patients randomised to drug and control—these are better designs but assume the new drug will benefit only biomarker 'positive' patients—to trials including both biomarker 'positive' and biomarker 'negative' patients randomised to drug and control—these are the preferred designs which attempt to maximise information about the predictive value of the biomarker.

Breaking with traditional statistical thought, it may be better to design phase II trials not to look for $p < 0.05$ in the comparison of drug to control, but to provide data that allows the likelihood of improved efficacy to be gauged both overall and in relation to the biomarker. Knowing, for example, from phase II that the likelihood of an improved outcome across all patients is, say, 80%, rising to 90% in those who were biomarker positive and slipping to 75% in those who are biomarker negative, a rational and informed decision could be made about how to precede in phase III. The design of phase II would then be driven not by hypothesis testing and concerns about showing significant differences, but more by the quantity of information it was desired to generate and the fraction of patients expected to be biomarker 'positive'.

With respect to phase III program design, there is a widespread belief that a biomarker selection strategy will result in smaller, more efficient and lower risk developments. However, this is not necessarily true in all cases. Two crucial assumptions frequently made to support this notion are (i) that the selected, biomarker 'positive' patients will experience a treatment effect while the unselected, biomarker 'negative' patients will be associated with no treatment effect and (ii) that the diagnostic that evaluates the biomarker is perfect, with 100% sensitivity and specificity. Maitournam and Simon provide a useful statistical basis for examining these issues [5].

For example, consider the situation described in Table 1.

Table 1. True median survival for new and control anti-cancer drugs

	Median survival on Control (months)	Median survival on New (months)	Treatment Effect HR* Control: New
Biomarker Positive (25%)	6 mo	12 mo	0.50
Biomarker Negative (75%)	6 mo	6 mo	1.00
All patients	6 mo	7.5 mo	0.80

* HR = Hazard ratio

Assuming a median follow-up of 18 months, it can be shown that a trial in all patients will require approximately

Table 2. The impact of an imperfect test

Sensitivity, Specificity	PPV*	Median survival on Control (months)	Median survival on New (months)	HR Control: New	N req'd to enter	N req'd to screen
100%, 100%	100%	6 mo	12 mo	0.50	117	468
95%, 75%	56%	6 mo	9.4 mo	0.64	260	613
75%, 95%	83%	6 mo	11 mo	0.55	149	663
75%, 75%	50%	6 mo	9 mo	0.68	317	845

* PPV= positive predictive value

Table 3. The impact of a small, non zero effect in biomarker 'negative' patients

	Median survival on Control (months)	Median survival on New (months)	Treatment Effect HR* Control:New	Number of patients required (screened)
Biomarker Positive (25%)	6 mo	12 mo	0.50	117 (468)
Biomarker Negative (75%)	6 mo	7.5 mo	0.80*	--
All patients	6 mo	8.7 mo	0.69	384 (384)

* Effect size in 'negative' patients = 1/3 effect size in 'positive' patients

1,000 patients to provide 90% power for a 1-sided 2.5% α level. However, if the trial selects only biomarker 'positive' patients, then only 117 patients would be required to achieve the same power, but 468 patients would have to be screened to allow for only 1 in 4 being biomarker 'positive'.

Table 2 shows how the efficiency gain in selecting only biomarker 'positive' patients is highly dependent on the performance of the diagnostic. With 75% sensitivity and specificity, the treatment effect is diluted by the erroneous inclusion of biomarker 'negative' patients, which consequently pushes up the sample size and the number need to screen so that, at 845 patients, we begin to approach the trial size required for the unselected approach.

In a similar fashion, Table 3 shows the impact of assuming a small treatment effect in biomarker 'negative' patients.

With a modest, non zero treatment effect in biomarker 'negative' patients, the number of patients required in the unselected trial reduces from 1000 to 384 so that the unselected trial requires fewer patients than are required to be screened for the selected design.

Thus, while it is clear that a biomarker directed development strategy can deliver efficiencies and greater security, much depends on how confident we are the biomarker is predictive as opposed to prognostic, the size of the treatment effect in biomarker 'negative' patients and the performance of the diagnostic. Violation of any one of these assumptions can quickly erode the value of a selected approach. This tends to underscore the importance of well-

designed phase II trials to provide data to investigate these crucial assumptions.

3. Moving on from patient selection - Biomarkers as endpoints to evaluate the relative effectiveness of new drugs

Moving on from patient selection, another key use for biomarkers in drug development is to employ the biomarker as endpoint. In considering the issues associated with this use of a biomarker, it is helpful to clarify (i) what stage of development are we in, what question is being asked and (ii) to what extent to drug induced effects on biomarker reflect a drug induced effect on clinical outcome.

The first of these questions is related to whether the decision we are making and, hence, the risk being taken is largely the sponsors (internal) risk or the regulators (external) risk. For example, using a biomarker to screen drug candidates early in development for likely efficacy or to choose between doses in phase II is largely the sponsor's risk. If an error is made, the use of the biomarker results in taking forward an ineffective agent or the wrong dose, the burden falls on the sponsor to rethink the development strategy. Little risk is borne by the regulator.

However, the use of biomarkers as substitute for clinical outcome for purpose of directly supporting approval is more troublesome. Here we are using the biomarker as a surrogate endpoint and a large part of the risk falls on the

regulator. The burden to demonstrate true surrogacy of an endpoint is known to be considerable. Statisticians know that simple correlation between the (assumed) surrogate and clinical outcome is a necessary, but insufficient condition to show surrogacy. Prentice [6] and Freedman [7] and, more recently, Buyse and Molenberghs [8-9], have provided a framework for assessing surrogacy, a framework that requires large, randomised controlled trials which capture both the (assumed) surrogate and clinical outcome – i.e., that require the very trials drug developers hope to avoid by use of the surrogate. PSA in prostate cancer illustrates how very difficult it can be to establish a biomarker as a surrogate endpoint. Despite more than 15 years of routine use in the management of patients with prostate cancer coupled with multiple large randomised, controlled trials looking at both PSA and clinical outcome and, more recently, formal published analyses [10] to examine surrogacy via the Buyse and Molenberghs method, PSA is still not accepted as an endpoint for drug approval. However, there is some hope – recent FDA workshops on cancer endpoints, including endpoints in prostate cancer, that may yet result in at least a composite endpoint that includes some component of PSA change as a measure of disease progression.

In a similar vein, longstanding clinical endpoints like progression-free survival in colorectal cancer are only just being accepted as endpoints for drug approval. This again is after years of use in the clinical management of patients and on the basis of multiple, well-controlled randomised trials that have recently been analysed to look formally at surrogacy for overall survival outcome.

So, set against this background, what realistic hope is there for novel biomarkers in new disease areas for their use as substitutes for clinical outcome in the evaluation of efficacy and safety and, ultimately, for drug approval?

The road for new biomarkers would therefore seem very difficult unless the level of evidence required to elevate a biomarker to surrogate endpoint status is lowered in some fashion. Many biomarkers in routine use today did not undergo rigorous evaluation for surrogacy using any kind of statistical criteria. For example, blood pressure, lipid lowering and response rate have all been used as primary endpoints to support drug approval, yet the evidence base for the surrogacy of these endpoints versus clinical outcome was not in hand. Rather, a judgement was applied at the time that a drug effect on these endpoints, whilst not being the ultimate clinical goal, was likely to reflect a (long term) benefit to the patient.

For some of the newer biomarkers emerging today and given current concerns over the long-term safety of drugs, there may be some reluctance to make the leaps of faith made in the past. This suggests that the best we can realistically hope for, at least initially, is biomarker endpoints to support approval meaning that trials which examine biomarker endpoints will likely still have to be designed and powered to examine accepted clinical endpoints. In due course, with experience and completed trials in hand, we might be able to move to a position where confidence with novel biomarker endpoints is such that they can form the basis of drug approval though, based on past performance, the timeframe may not be a quick as some would wish.

In summary, biomarkers are increasingly important tools in the drug development process and in helping to formulate drug development strategies. With the right biomarker in hand, patient selection strategies can result in smaller, less costly and more secure developments but there are crucial assumptions that must be highlighted and tested. Experienced statistical input

to aid in the design phase II trials to evaluate these assumptions and guide phase III development is crucial. The use of biomarkers as endpoints per se is also important going forward. Where their use is for internal decision making purposes, there seems little impediment to their use and the burden falls squarely on the sponsor to be sure the biomarker endpoint helps to make the right, not the wrong decisions. However, using biomarkers as surrogate endpoints for clinical outcome to support drug approval is more troublesome. Establishing a new biomarker as a true surrogate endpoint using published statistical criteria is extremely demanding, if not impossible. This suggests acceptance of a lower burden of evidence is required and, consequently, that greater risks must be taken, in order to use new biomarkers as substitutes for clinical outcome. At the present time and in the present climate, the likelihood of this seems rather remote. In due course, however, with experience and completed trials in hand, biomarker endpoints may well form the basis of drug approval though the timeframe for acceptance of surrogacy may not be a quick as we might wish. ■

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Bayesian Adaptive Design Method with Biomarkers

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Summary: Biomarkers, as compared to a true endpoint such as survival, can often be measured earlier, easier, and more frequently; are less subject to competing risks, less confounded by other treatments, reduce sample size required due to a larger effect size; and lead to faster decision-making. Challenging issues in the validation of biomarkers are discussed here. Adaptive design methods using biomarkers are proposed. The Bayesian optimal approach is also discussed.

Keywords: Biomarker, Adaptive design, Bayesian, Sequential design.

1 Introduction

The FDA's "Critical Path Opportunities List" emphasizes the importance of the framework and evidence needed to qualify biomarkers in drug development. It is pointed out that consensus on the following questions is needed to put the framework in place (FDA, 2006):

(1) How can biomarker evidence help demonstrate that a candidate product is not too toxic to test in humans?

(2) How can biomarkers be used to select dose ranges for initial human testing?

(3) How can biomarkers be used most effectively to evaluate dose response in later trials?

(4) What biomarker evidence is appropriate to guide selection of patients for clinical testing?

(5) What types and levels of evidence are needed to accept a biomarker as a surrogate endpoint for product efficacy? In this paper, we will discuss the challenges of biomarker validation and potential uses for biomarkers in clinical trials using adaptive methods. Through this discussion, we hope to provide some insight into what is really needed to qualify a biomarker. In what follows, we will briefly review some biomarker-related definitions and the importance of biomarkers. We will then discuss the potential issues that arise when using biomarkers with a classic design. Challenges in the validation of biomarkers are discussed through the Treatment-Biomarker-Endpoint 3-way relationship and multiplicity. Validation methods for biomarkers are briefly reviewed. Examples of adaptive designs with classifier and predictive biomarkers are provided. Optimization of design using Bayesian is demonstrated. Concluding remarks are also presented.

1.1 Definitions

There is some confusion regarding the terms "biomarker" and "surrogate marker." In this paper, we will use the following definitions:

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention (Chakraverty, 2005). **Surrogate:** A laboratory or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy (Temple, 1999). A surrogate is a subset of biomarkers that is expected to predict clinical benefit (or harm, or lack of benefit or harm) based on epidemiologic, therapeutic,

pathophysiological or other scientific evidence (Chakraverty, 2005). **Clinical or true endpoint:** The gold standard endpoint, such as survival in oncology trials

It is helpful to differentiate two different types of biomarkers: The first, called classifier biomarkers, would be stable during the treatment course like DNA markers; the others, called predictive biomarkers, would change over the course of treatment over time like RNA markers.

1.2 Why Biomarkers?

The classifier biomarker can be used to select the most appropriate target population or even for personalized treatment. For example, a study drug is expected to have effects on a population with a biomarker, which is only consistent for 20% of the overall patient population. Because the sponsor doubts that the drug will work for the overall patient population, it may be efficient and ethical to run a trial only for the subpopulations with the biomarker rather than the general patient population.

The predictive biomarker, as compared to true endpoints like survival, can often be measured earlier, easier, and more frequently and is less subject to competing risks. For example, in a trial of a cholesterol-lowering drug, the ideal endpoint may be death or development of coronary artery disease (CAD). However, such a study usually requires thousands of patients and many years to conduct. Therefore, it is desirable to have a biomarker, such as a reduction in post-treatment cholesterol, if it predicts the reductions in the incidence of CAD. Another example would be an oncology study where the ultimate endpoint is death. However, when a patient has disease progression, the physician will switch the patient's initial treatment to an alternative treatment. Such treatment modalities will jeopardize the assessment of treatment effect on survival because the treatment switching is response-adaptive rather than random. If a biomarker, such as time-to-progression (TTP) or response rate (RR), is used as the primary endpoint, then we will have much cleaner efficacy assessments because the biomarker assessment is performed before treatment switching occurs.

1.3 Classic Design with Biomarker Endpoint

Given the characteristics of biomarkers, it is natural to think to design a trial using a biomarker. Can we use a biomarker as the primary endpoint for late-stage or confirmatory trials? Let's study the outcome in three different sce-

narios. (1) Treatment has no effect on the true endpoint or the biomarker. (2) The treatment has no effect on the true endpoint but does affect the biomarker. (3) The treatment has a small effect on the true endpoint but has a larger effect on the biomarker. Table 1 summarizes the type-I error rates (α) and powers for using the true endpoint and biomarker under different scenarios. In the first scenario, we can use either the true endpoint or biomarker as the primary endpoint because both control the type-I error. In the second scenario, we cannot use the biomarker as the primary endpoint because α will be inflated to 81%. In the third scenario, it is better to use the biomarker as the primary endpoint from a power perspective. However, before the biomarker is fully validated, we don't know which scenario is true; the use of the biomarker as the primary endpoint could lead to dramatic inflation of the type-I error, i.e., efficacy of the drug could be inferred but in fact it has no efficacy at all.

Table 1: Power (Type-I Error) of Hypothesis Testing with Classic Design Based On True-Endpoint and Biomarker

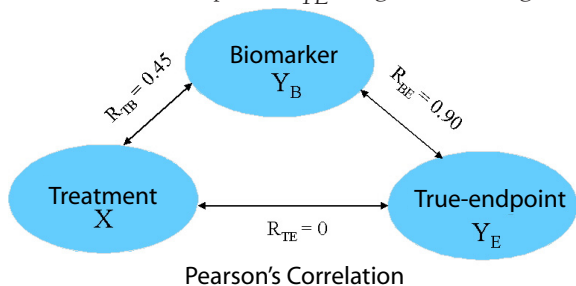
Effect size ratio	Endpoint	Power (alpha)
0.0/0.0	True Endpoint	(0.025)
	Biomarker	(0.025)
0.0/0.4	True Endpoint	(0.025)
	Biomarker	(0.810)
0.2/0.4	True-Endpoint	0.300
	Biomarker	0.810

Note: N = 100 per group. Effect size ratio = effect size of true endpoint to effect size of biomarker.

2 Challenges in Validation of Biomarkers

2.1 Treatment-Biomarker-Endpoint Relationship

Before we discuss biomarker validations, let's take a close look at the 3-way relationships among treatment, biomarker and the true endpoint. It is important to be aware that the correlations between them are not transmittable. In the following example, we will show that it could be the case that there a correlation between treatment and the biomarker (R_{TB}) and a correlation between the biomarker and the true endpoint (R_{BE}), but there is no correlation between treatment and the true endpoint (R_{TE}) (Figure 1 and Figure 2).



Regression: $Y_T = Y_B - 2 X$

Figure 1: Treatment-Biomarker-Endpoint Three-Way Relationship

The hypothetical example to be discussed is a trial with 14 patients, 7 in the control group and 7 in the test group. The biomarker and true endpoint outcomes are displayed in Figure 2. The results show that the $R_{BE} = 1$ in both groups. If the data are pooled from the groups, the correlation between the biomarker and the true endpoint is still high, about 0.9. The average response with the true endpoint is 4 for each group, which indicates that the drug is ineffective compared with the control. On the other hand, the average biomarker response is 6 for the test group and 4 for the control group, which indicates that the drug has effects on the biomarker.

Facing the data, what we typically do is to run a regression model with the data where the dependent variable is the true endpoint (Y_T) and the independent variables (predictors) are the biomarker and the treatment. After model fitting, we can obtain that

$$Y_T = Y_B - 2X \quad (1)$$

This model fits the data well based on model-fitting p-value and R^2 . Specifically, R^2 is equal to 1, p-values for model and all parameters are equal to 0, where the 2 in (1) is the separation between the two lines. Therefore, we would conclude that both biomarker and treatment affect the true endpoint. However, we know that the treatment has no effect on biomarker at all. In fact, the biomarker predicts the response in the true endpoint, but it does not predict the treatment effect on the true endpoint.

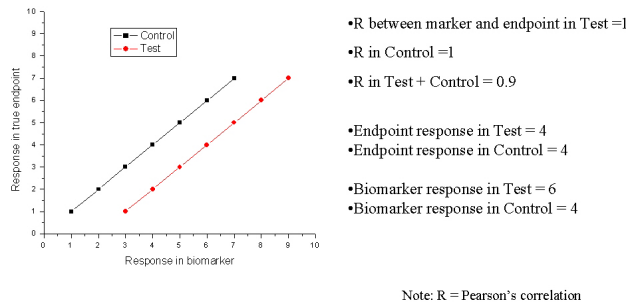


Figure 2: Correlation Is Not Prediction

2.2 Multiplicity and False Positive Rate

Let's further discuss the challenges from a multiplicity point of view. In earlier phases or the discovery phase, we often have a large number of biomarkers to test. Running hypothesis testing on many markers can be done either with a 5 high false positive rate without multiplicity adjustment or a low power with multiplicity adjustment. Also, if model selection procedures are used without multiplicity adjustment as common practice, the false positive rate could be inflated dramatically. The other source of false positive discovery rate is the so-called publication bias. The last, but not least, source of false positive finding is the multiple testing conducted by different companies or research units. Imagine that 100 companies study the same biomarker; even if family-wise type-I error rate is strictly

Freedman, et, al. (1992) argued that the last Prentice criterion is difficult statistically because it requires that the treatment effect is not statistically significant after adjustment of the surrogate marker.

controlled at a 5% level, there will still be, on average, 5 companies that have positive findings about the biomarker just by chance.

2.3 Validation of Biomarkers

We now realized the importance of biomarker validation and would like to review some commonly used statistical methods for biomarker validation.

Prentice (1989) proposed four operational criteria: (1) Treatment has a significant impact on the surrogate endpoint, (2) Treatment has a significant impact on the true endpoint, (3) the surrogate has a significant impact on the true endpoint, and (4) the full effect of treatment upon the true endpoint is captured by the surrogate endpoint. Note that this method is for a binary surrogate (Molenberghs, 2005). Freedman, et, al. (1992) argued that the last Prentice criterion is difficult statistically because it requires that the treatment effect is not statistically significant after adjustment of the surrogate marker. They further articulated that the criterion might be useful to reject a poor surrogate marker, but it is inadequate to validate a good surrogate marker. Therefore they proposed a different approach based on the proportion of treatment effect on true endpoint explained by biomarkers and a large proportion required for a good marker. However, as noticed by Freedman (2001), this method is practically infeasible due to the low precision of the estimation of the proportion explained by the surrogate. Buyse and Molenberghs (1998) proposed the internal validation matrices, which include relative effect (RE) and adjusted association (AA). The former is a measure of association between the surrogate and the true endpoint at an individual level, and the latter expresses the relationship between the treatment effect on the surrogate and on the true endpoint at a trial level. The practical use of the BM method raises a few concerns: (1) A wide confidence interval of RE requires a large sample size; (2) Treatment effect on the surrogate and the true endpoint are multiplicative, which cannot be checked using data from a single trial. Other methods, such as external validation using meta-analysis and two-stage validation for fast track programs, also face similar challenges in practice.

2.4 Biomarkers in Reality

In reality, there are many possible scenarios: (1) same effective size for the biomarker and true endpoint, but the

biomarker response is earlier, (2) bigger effective size for the biomarker and smaller for the true endpoint, (3) no treatment effect on the true endpoint, limited treatment effect on the biomarker, and (4) treatment effect on the true endpoint only occurs after the biomarker response reaches a threshold. Validation of biomarkers is challenging, and the sample size is often insufficient for the full validation. Therefore validations are often performed to a certain degree. Soft validation scientifically (e.g., pathway) is important. What is the utility of partially validated biomarkers? In the next section, we will discuss how to use biomarkers in adaptive designs.

3. Adaptive Design with Biomarker

An adaptive design is a design that allows adaptations or modifications to some aspects of the trial after its initiation without undermining the validity and integrity of the trial (Chow, Chang & Pong, 2005; Chang, Chow & Pong, 2006). The adaptations may include, but are not limited to (1) hypothesis change, (2) sample size re-estimation, (3) early stopping due to efficacy or futility, (4) response-adaptive randomization, and (5) dropping inferior treatment groups.

3.1 Design with Classifier Biomarker

As mentioned earlier, a drug might have different effects in different patient populations. In this example, the sponsor faces the dilemma of whether to target the general patient population or use biomarkers to select a smaller set of patients that would more likely have a response to the drug. At the design stage, we don't know exactly the treatment effect sizes for the general patient population and the subpopulation with the biomarker. To design the trial, the utility function has to be constructed first. There are many utility functions to choose from. For example, the utility is defined as $U = (\sum \delta_i N_i - C_i)$, where δ_i is the effect size of the i^{th} subpopulation with the size of N_i and C_i is the associated cost. A hypothetical scenario is presented in Table 2:

Table 2: Utility for Different Patient Populations

Biomarker	Population size	Effect size	Utility
Positive	25% (1 M)	1.0	0.25
Negative	75% (3 M)	0.2	0.15
Overall	100% (4 M)	0.4	0.40

There are several challenges: (1) The estimated effect size for each sub-population at the design stage is very inaccurate; (2) A cost is associated with screening patients for the biomarker; (3) The test for detecting the biomarker often requires high sensitivity and specificity, and the screening tool may not be available at all; (4) Screening patients for the biomarker may cause difficulties in recruiting patients. These factors must be considered in the design.

To handle the challenges, we start with the overall patient population and the adaptive design with one interim look. At interim look, we make a decision of whether to go for the subpopulation or the overall population based on the expected utilities in each scenario:

(1) If we target the subpopulation with the biomarker, the expected utility is given by

*(conditional power of subpopulation at interim look) * (Impact of success) - (1-conditional power of subpopulation at interim look) * (Impact of failure)*

(2) If we target the full patient population with the biomarker, the expected utility is given by

*(conditional power of full population at interim look) * (Impact of success) - (1-conditional power of full population at interim look) * (Impact of failure)*

Various statistical methods can be used for this adaptive design, such as stagewise p-value combinations (Bauer & Kohne, 1994, 1995; Muller & Schafer, 2001; Posch & Bauer, 2000; Proschan & Hunsberger, 1995; Proschan & Wittes, 2000; Todd, 2003; and Chang, 2005), but the details of this are beyond the scope of this paper.

3.2 Design with Predictive Biomarker

In this example, we discuss how to use a predictive biomarker in trial design. The adaptive design proposed permits early stopping for futility based on the interim analysis of the biomarker. At the final analysis, the true endpoint will be used to preserve the type-I error. Assume there are three possible scenarios: (1) H_{01} : Effect size ratio ESR = 0/0, H_{02} : Effect size ratio ESR = 0/0.25, and (3) H_a : Effect size ratio ESR = 0.5/0.5, but biomarker response earlier, where is the ESR is the ratio of effect size for true endpoint to the effect size for biomarker. We have compared 3 different designs: classic design and two adaptive designs with different stopping boundaries as shown in Table 3, where Z is the Normal test statistic.

We can see that the first adaptive design can save sample size under the null hypothesis. However, this comparison is not good enough because it does not consider the prior distribution of each scenario, i.e., the likelihood of H_{01} ; H_{02} ; and H_a at the design stage. Next we will consider a Bayesian approach to selecting an optimal design.

Table 3: Adaptive Design with Biomarker

Design	Condition	Power	Expected N/arm	Stopping Boundary
Classic	H_{01}		100	
	H_{02}		100	
	H_a	0.94	100	
Adaptive	H_{01}		75	Z=0.0
	H_{02}		95	
	H_a	0.94	100	
Adaptive	H_{01}		55	Z=1.25
	H_{02}		75	
	H_a	0.85	95	

3.3 Bayesian Optimal Design

We have noticed that there are many different scenarios with associated probabilities (prior distribution) and many possible adaptive designs with associated probabilistic outcomes (good and bad). We have also formed the utility function and the criteria for evaluating different designs. Now let's illustrate how we can use Bayesian utility theory to select the best design under financial, time, and other constraints. First assume the prior probability for each of the scenarios mentioned earlier (table 4).

Table 4: Prior Knowledge about Effect Size

Scenario	Effect Size	Prior
	Ratio	Probability
H_{01}	0/0	0.2
H_{02}	0/0.25	0.2
H_a	0.5/0.5	0.6

For each scenario, we conducted computer simulation to calculate the probability of success and the expected utilities for each design. The results are summarized in Table 5.

Table 5: Expected Utilities of Different Designs

Design	Classic Biomarker-Adaptive	
	Z = 0	Z = 1.25
Expected Utility	419	411

Based on the expected utility, the adaptive design with the stopping boundary Z = 0 is the best. Of course, we can also generate more designs and calculate the expected utility for each design and select the best one.

4. Summary

Full validation of a biomarker is statistically challenging. Sufficient validation tools are not available and may never be available. Adaptive design using biomarkers can be beneficial even when the biomarkers are "softly" validated. The Bayesian approach is an ideal solution for finding an optimal design. Computer simulation is a powerful tool for the utilization of biomarkers in trial design. ■

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2006 FDA/Industry Workshop, September 27-29, Washington, DC

Richard Kotz,
FDA and Lee Kaiser, Genentech

This three-day workshop is sponsored by the ASA Biopharmaceutical Section in cooperation with the FDA Statistical Association. It will be held September 27-29 at the luxurious Marriott Wardman Park Hotel in Washington D.C. Short courses are scheduled on the first day, September 27, followed by two days of sessions on the science and statistics associated with the development of new medical products—pharmaceuticals, biologics and devices. The workshop has been very popular since its inception because it is designed specifically to bring together statisticians from industry, academia, and the FDA, and it provides a unique opportunity for open dialogue on issues of mutual interest.

The theme of this year's workshop is Statistics in the FDA and Industry: Past, Present, and Future. The year 2006 marks the 100th anniversary of the U.S. Food and Drug Administration and the 30th anniversary of the 1976 Medical Device Amendments to the Food, Drug, and Cosmetic Act. In recognition of these milestones, one session will describe how the current regulatory environment came to be, from an FDA and an industry perspective, and speculate, too, on the future contribution of statistics to drug and device development. Other planned plenary and parallel sessions will address a wide variety of important, timely issues, including high dimensional expression data quality and consistency; use of historical control data in product development; Bayesian clinical trials; decision analysis in clinical trials; guidance for diagnostic device development; statistics in post-marketing; statistical issues in medical device trials; combination treatment-diagnostics submissions; rare event estimation with insurance claims databases; flexible clinical trials; assessing agreement; bridging studies; interpreting subgroup results in regulatory submissions; surrogate endpoints and accelerated approval; CDISC, standards, and communicating with FDA; modeling and simulation; and quality by design. The planned short courses will cover Bayesian clinical trials, adaptive clinical trials, surrogate variables, and the GLMM and GLIMMIX SAS procedures. Based on the continued positive feedback from previous attendees, luncheon roundtables, with moderated discussion of a wide variety of topics, will be take place on Thursday, September 28.

The Marriott Wardman Park Hotel is a premier meeting site located in a convenient, historic setting in Washington D.C. Covering 16 rolling acres of gardens and woodland, the hotel is perched on a small bluff overlooking Rock Creek Park. There is an on-site Metro stop, and it is within walking distance of the National Zoo and within eight miles of Reagan National Airport. A block of sleeping rooms has been arranged for workshop attendees. To receive the special workshop rates, attendees must book their reservations by August 27. Please visit www.amstat.org/meetings/fdaworkshop for the preliminary program, a list of workshop organizers, the registration form, and information on hotel reservations. The FDA/Industry Statistics workshop is a unique forum for statisticians at FDA and in industry to discuss topics of mutual interest. Be a part of it! ■

Summary of the Executive Committee Meeting of the Biopharm Section, March 28, 2006

Attendees: Stacy Lindborg, Margaret Minkwitz, Amit Bhattacharyya, Brian Wiens, Andy Mugglin, Joe Heyse, Richard Caplan, David Manner, Christie Clark, Steve Gulyas, Anna Nevius, Kieth Soper; via Teleconference: Kalyan Gosh, Kay Larrholt, J. Colaianne, Russell Helms, Michael Hesney, Steve Snapinn, Shuguang Huang, Mani Lakshiminarayanan, Aparna Raychaudhuri, Lei Zhu, Len Openheimer, Mark Chang, Philip Pichotta

Treasurer's Report: We have a positive balance in the treasury, and although the surplus has not yet reached the level of concern, the executive committee decided to evaluate options to use some of these funds to better serve our membership. Ideas generated included offering a Web Cast course or videotaping our JSM courses for use by our membership, these ideas are being developed as proposals for discussion at subsequent meetings of the Executive Committee in 2006.

Nominations Committee Report: The charter was changed in 2003 to separate the position into two 3-year positions with staggered elections. On the 2005 election ballot, a miscommunication occurred and the secretary was not included on the ballot. We don't want to have the election for treasurer and secretary next year. One option is for the Chair to make an appointment (which can occur for any open position). A suggestion was made to appoint Devon Mehrotra to the position. He was one of the 2 members the nomination committee places on the election ballot in 2005.

Mani has been appointed to serve as treasurer 2006 - 2007. The election for Treasurer will occur in 2007 for a term spanning 2008-2010. Devon Mehrotra will be appointed as Secretary by Stacy for 2007-2008. The election for Secretary will occur in 2008 for a term spanning 2009-2011. Approved by acclamation.

Biopharm Report: Richard Caplan is planning future issues and recommended that we consider requesting a brief report from Round Table Discussion chairs from the JSM meeting for inclusion in the Report. Timely minutes of Executive Meetings are planned to be included. Richard also requested ideas and authors (send names), topics, helpful articles be sent to him at richard.caplan@astrazeneca.com.

Corporate Sponsorship: J. Colaianne reported that as of the meeting we had sponsorship from 14 companies, for a total of \$13,750; about half of last year's support level.

ASA Journal of Biopharmaceutical Research Report: Joe Heyse has been named the first editor of the Journal. The first issue is expected to come out in 2007, it is planned to be quarterly and approximately 100 pages per issue. The key success factor will be serving the needs of the Biopharm Section. The committee is setting up a web based submission and tracking system (alentrack system). There are expected to be 12 associate editors in place by the end of April 2006. Consider papers you might have which-

would fit into this journal. The system should be available for submission later in 2006.

Report from Meeting Chair on the JSM meeting: The section will be sponsoring 39 sessions at the 2006 JSM Meeting; 7 invited, 12 topic contributed, 20 contributed. We will have 40 round table luncheons, 13 on Monday, 14 on Tuesday and 13 on Wednesday. Proposals for the 2007 meeting invited sessions, with speakers identified, need to be in by May 15, 2006.

Report on the FDA/Industry Workshop: The 2006 FDA/Industry Workshop is entitled "Statistics in the FDA and Industry: Past, Present and Future" will be held Sept 27-29 at the Wardman Park Hotel in Washington, DC. There are 4 short courses planned as well as sessions, general, parallel and round table luncheons.

Action: Committees to bring forward proposals at the August meeting as to feasibility and costs of a Web Cast course and videotaping of short course offerings sponsored by the Section at JSM or the FDA/Industry Workshop.

Action: The Operations Manual is out of date, Committee Members were requested to review the manual for their position and come to JSM with updates for discussion. ■

JSM 2006 Luncheon Roundtables

Amit Bhattacharyya

The Biopharmaceutical section is sponsoring a record number (40) of luncheon roundtables during Monday, Tuesday and Wednesday at the JSM 2006. The topics range from different phases of drug discovery and development, interactions with FDA and issues related to devices. Many industry, academic and regulatory statisticians are leading these topics. Attendance to these luncheons does not require membership of the section. Because attendance to these luncheons is on a first-come-first-served basis, members are encouraged to sign up early for the roundtables that they desire. Members should encourage their colleagues to sign up for relevant roundtables as well. ■

Let's Hear from You!

If you have any comments or contributions, contact the Editor: Richard Caplan, phone: 302-885-5915, email: richard.caplan@astrazeneca.com; or Associate Editor: Philip Pichotta, phone: 203-882-9321, email: pichottapm@optonline.net.

We are looking for volunteers to write articles that will be of interest to our members. Some authorless topics that have been suggested include validating endpoints and working with SEALD, enhanced trial designs, animal studies and veterinary medicine, bioequivalence in biologics and personalized medicine. Non-technical articles related to our work are welcome. If you have been working in an area and would like to suggest a topic or volunteer to write, please send us an email.

The Biopharmaceutical Report is a publication of the *Biopharmaceutical Section* of the American Statistical Association.

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