Application of Biomarkers, Surrogate Endpoints, and Correlates of Protection to Vaccine Development

**Biomarkers:**

Biomarkers are substances, structures, or processes that can be measured in biological samples such as urine, blood, or saliva. A biomarker is a measurable characteristic in a biological system that changes due to disease, exposure to chemicals, or exposure to organisms. Biomarker evaluation requires an understanding of the differences among measurements of the cause of a disease, risk factors for outcome, and measurements of intervention effects. Whatever biomarker is selected, it must be under the influence of the therapy/intervention and represent an important part of the causal pathway leading from the introduction of vaccine to the clinical endpoint (disease). Biomarkers have always been important in clinical development and provide the most practical means of demonstrating that a candidate drug is safe and effective in a disease target population.

**Surrogate Endpoints:**

Surrogate endpoints are markers of biological mechanisms (i.e., biomarkers) that predict a clinical benefit, substitute for a clinical endpoint, and provide a mechanistic view on diseases (i.e., direct measurement of how a patient feels, functions, or survives). Surrogate endpoints are considered minor outcome measures that are easier to record and are, thus, being adopted instead of major (hard) endpoints that currently constitute the gold standard in the definition of outcome measures. Therefore, a surrogate endpoint may be defined as any parameter that can be used to measure an interaction between a biological system and an environmental agent, which may be chemical, physical, or biological. Randomized, blinded, controlled clinical trials with definitive endpoints represent the “gold standard” by which new vaccines and drugs are judged. To accelerate the development and licensure of a vaccine, without the use of expensive and laborious efficacy trials, requires the availability of laboratory markers of immunity that can reliably predict clinical protection. Such markers or surrogate endpoints may measure a specific antibody or cellular immune response associated with a well-controlled phase III efficacy trial that represents the protective effect in an individual against clinical disease.

A. General Characteristics of Biomarkers/Endpoints

- Surrogate endpoints are intended to substitute for a clinical endpoint/outcome such as the prevention of disease and/or infection and are expected to predict clinical benefit or lack of benefit.
- Surrogate endpoints associated with vaccine evaluation are usually categorized as either: 1) clinical; 2) pathophysiological; 3) immunological; or 4) epidemiological.
- Biomarkers represent a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes to a therapeutic or vaccine intervention.
• Biomarkers can be characterized as a functional measure associated with a mode of protection.
• Biomarkers are used to identify subgroups of patients who respond to therapies and interventions in different ways. Biomarkers are also used to aid in the early detection of disease and in the investigation of therapies/interventions aimed at reducing the risk of disease.
• Surrogate endpoints are often used to screen candidate vaccine interventions by substituting for a primary endpoint of Phase III trials. Generally, biomarkers are used in situations where trials, employing clinical endpoints, are not feasible or cannot be carried out efficiently and inexpensively? Trials evaluating new pneumococcal vaccines in the U.S. fall into such a category.

B. Advantages of Biomarkers/Endpoints

• Surrogate endpoints are detected earlier or more readily than corresponding hard clinical outcomes and, therefore, reduce the need to achieve hard clinical endpoints in clinical trials. In addition, they are obtained on a smaller clinical scale and less invasively than the true endpoints for a given health outcome.
• Biomarkers are increasingly being used by researchers associated with industry, universities, and government and have proven to be cost-effective and reliable for the purpose of monitoring, developing, and predicting efficacies for both drugs and vaccines.

C. Important Features of Biomarkers/Endpoints

• Current regulations permit the FDA to base the approval of a drug on a determination of the effect the drug has on a validated surrogate marker.
• The FDA has also stated that it will accept immunogenicity data in support of licensure in lieu of traditional vaccine efficacy studies for new candidate pneumococcal vaccines.
• ICH guidelines on Statistical Principles for Clinical Trials state that “In practice, the strength of the evidence for surrogacy depends upon (1) the biological plausibility of the relationship; (2) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome; and (3) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome.
• Biomarkers and biomarker assays require validation. To be considered as acceptable substitutes for hard endpoints, one must have confidence that changes in the biomarker are clinically meaningful and reliably predict the effect of the treatment/intervention on the desired clinical endpoint of interest based on epidemiologic, therapeutic, pathophysiologic, pharmacologic, or other evidence.
• The use of surrogate endpoints requires that consideration be given to conducting long-term clinical follow-up to demonstrate the effect of such biomarkers on disease progression.
• Evaluation of biomarkers as surrogate end points poses distinct challenges and difficulties. Thus, when considering the use of surrogate endpoints as primary
measures, these challenging issues must be addressed to avoid compromising what is truly in the best interest of public health.

**Immunological Correlates of Protection:**

Immunological correlates of protection represent a predictable relationship, based on a statistical probability, which says that if one thing happens, something else related will follow. A major objective of vaccine research is to identify a vaccine-induced immune response or a surrogate serologic test that predicts protection from infection or disease. Such responses are mainly used to predict the vaccine’s protective effect in a new setting, for which vaccine efficacy is not directly observed.

A correlate of protection usually represents a laboratory parameter (e.g., substantial levels of high affinity antibodies to one or more important bacterial or viral antigens) that is correlated with protection against disease and, therefore, is correlated with the surrogate or biomarker. Unlike the biomarker, the correlate of protection is not a direct measure of either antibody or cellular activity that is mediating protection. Correlates of protective immunity to bacterial and viral pathogens in humans are desirable for: 1) identifying protective antigens; 2) demonstrating the immunogenicity of a candidate vaccine and its potential efficacy; and 3) permitting optimization of the dose, vehicle, adjuvant, and schedule of immunization. Potential correlates can be proposed on the basis of animal models and clinical studies in humans. The validation of a protective correlate is critical and requires correlation with protection to a phase III efficacy trial for an effective vaccine. Correlates of protection are also best measured using a functional bioassay such as opsonophagocytosis (OPA) rather than a non-functional assay such as ELISA. Once a biomarker or immunological endpoint is established, an immune correlate of protection for vaccine efficacy may be identified by analyzing results from a successful efficacy trial with clinical endpoints. According to the FDA, an immunological correlate for protection is most useful if clear qualitative and quantitative relationships can be determined that have the capacity to both predict and afford protection from disease.

**Value to Vaccine and Drug Development:**

Because the resources needed to develop and evaluate new drugs and vaccines are increasing dramatically, the number of approved new drugs and vaccines is on the decline. Vaccine and drug manufacturers, desperate for ways to expedite the drug and vaccine development process while decreasing expenses, are turning to biomarkers as one possible solution. Biomarkers serve to establish an immunologic pathway to licensure other than efficacy trials and in so doing, play a critical role in making efficacious and cost-saving decisions.

The bottom line is that the absence of apparent immune correlates can pose a significant obstacle to vaccine research and development. Without knowing more about the quantity and quality of antibodies needed for protection against disease and carriage, the only method of assessing vaccine effectiveness will be through large phase III trials with clinical outcomes rather than the use of cost-effective laboratory markers. The potential
of a biomarker, thus, further allows a company to have greater confidence in selecting its products for development and mapping out future directions. Overall, biomarkers represent a significant research tool that allow for the earlier identification of health effects a candidate vaccine or therapeutic has on a given population and permits the evaluation of new vaccines more efficiently.