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Driving Development

Suzanne M Sensabaugh at MDS Pharma Services recognises the advantages of expediting drug development through the use of biomarkers

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Biological markers, or biomarkers, play a pivotal role in a successful biopharmaceutical development programme. Biomarkers enable each step of the process – from discovery and preclinical development to the clinic and finally to market – and can assist in streamlining and expediting the drug development process.

Biomarkers are defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention (1). Biomarkers are qualitative measures of biological effects that provide links between the mechanism of action and clinical effectiveness (2). This link can assist companies in evaluating the biological response to a novel biopharmaceutical in each stage of development. The drug development process is a methodical process in which the results of each step lead to the development of a hypothesis and testing strategy for the next step. Biomarkers can assist companies in the development and design of hypothesis testing. The results of each step require analysis and 'go/no go' decision-making prior to passing to the next phase of development.

Biomarkers are considered to be an additional variable in the design of preclinical and clinical trials, which may contribute to the rate of trial success. A successful outcome may result in faster time-to-market for the product and/or the avoidance of the inclusion of trial subjects who have a low probability of responding to the biopharmaceutical product. In fact, the European Medicines Agency (EMEA) cites biomarkers as key to "the right drug at the right dose in the right patient group" approach (3). Success may also be measured in halting a drug with no promise of reaching the market as early in the drug development process as possible. A new product entering Phase I testing is estimated to have only an eight per cent chance of reaching the market (4), and drug failures account for 75 per cent of cumulative research and development cost (5). Therefore, the use of biomarkers can lead to capital resource savings and reduce the risk of late phase attrition through the removal of a product from the development pipeline as early as possible prior to the product's eventual failure.

BIOMARKERS IN EACH STEP OF THE DEVELOPMENT PROCESS

The successful application and use of biomarkers can facilitate the drug development process at every phase. Biomarkers are used in *in vivo* models during discovery to identify lead candidates for further development. Formulations can also be evaluated early on to ensure that an excipient does not have a potentially adverse effect on safety and effectiveness, or a company may desire the opposite situation where an excipient has an adjuvant effect.

Biomarkers are used to examine safety and identify potential indicators of effectiveness in animal models. Defining and interpreting development-limiting toxicity can be assisted by biomarkers through the investigation of the nature of the toxicity in preclinical studies and its reversibility. The earlier a company can identify product-limiting toxicity in an animal model that predicts clinical-limiting toxicity, the earlier the molecule can be removed from the development pipeline (6). Biomarkers can lead to a better understanding of the biological

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mechanism of action through the monitoring of the resultant effect. Biological activity can be monitored during *in vivo* preclinical studies to enable dose selection for early clinical development. For biopharmaceuticals, the use of the minimum anticipated biological effective dose (MABEL), rather than the no observed adverse event level (NOAEL), is suggested for dose selection for initiation of a first-in-human trial (7). The transition to clinical development from preclinical is one of the most critical phases of drug development.

During clinical Phases I and II, biomarkers can provide evidence that a molecule has bound to and modified its target, resulting in a demonstration of biological activity. This is especially useful for providing early testing of hypotheses, particularly if these changes can be measured in healthy volunteers. Companies use biomarkers to conduct initial proof-of-concept (POC) studies in patients to investigate signals of effectiveness prior to conducting extensive formal studies for regulatory approval. These POC studies assist in prioritising drug development resources as well as providing results to potential investors, such as venture capitalists or licensees. Biomarkers also assist in establishing dose-response relationships resulting from dose-finding studies, allowing quantification of target modulation. This relationship can be used to further define dosing for the Phase III study.

Pharmacodynamic biomarkers can be used to explore biological activity in preclinical studies, enable the transition into clinical development, and aid in providing support to efficacy. For example, epoetin alfa and beta (Aranesp® and Epogen®, Amgen; EPREX®, J&J; NeoRecorman®, Roche; Procrit®, OrthoBiotech) stimulate red blood cell production. Distinct pharmacodynamic biomarkers of erythrogenesis – such as level of haemoglobin, haematocrit value and reticulocyte count – are used in preclinical and clinical trials to investigate the biological response. Somatropin (Genotropin®, Pfizer; Humatrope®, Lilly; Norditropin®, Novo Nordisk; Nutropin®, Genentech; Omnitrope®, Sandoz; Saizen®, Serono; Tevtropin®, Teva Pharmaceuticals; Valtropin®, Biopartners) stimulates the liver to produce insulin-like growth factor-1 (IGF-1), a biomarker. In patients who are growth hormone-deficient, IGF-1 biological activity is measured as a downstream indicator of response to replacement therapy.

Phenotypic or genotypic biomarkers can assist in the prediction of the outcome of a clinical trial and support trial population selection strategies. Biomarkers can aid in segmenting a population and stratifying patients to enhance Phase III trials. Defining a subset of patients who respond to therapy can turn a potentially failed clinical trial into a successful one for the specific cohort of patients. Enhancing clinical trials with a population of patients who are better responders can also lead to reducing the size of the trial required to detect efficacy, and possibly even shortening observation times. Today, drugs that target specific receptors and genotypes are being developed. These drugs have clinical biomarkers that are linked to drug efficacy. HER2/neu overexpression serves as both a marker of aggressive breast cancer and a target for treatment. Trastuzumab (Herceptin®, Genentech), a humanised monoclonal antibody against HER2, was developed with this specificity in mind. Testing of tumours for expression of HER2 was integral to the selection of patients for clinical trials to demonstrate the efficacy of trastuzumab. In chronic myelogenous leukemia, an inter-chromosomal exchange leads to the creation of a gene (BCR-ABL) which expresses a protein with elevated tyrosine-kinase activity. Imatinib mesylate (Gleevac®, Novartis) inhibits this kinase. The BCR-ABL-positive tyrosine kinase genotype was used to identify patients who are likely to respond to treatment with Gleevac.

The use of biomarkers can also avoid exposing individuals to drugs and doses which are not likely to be beneficial, but also which might be toxic. A clinical biomarker that is linked to drug toxicity is a genetic polymorphism of UDP-glucuronosyltransferase 1A1 enzyme (UGT1A1). A reduction in this enzyme is seen in patients homozygous for this mutation. Irinotecan (Camptosar®, Pfizer), an anticancer drug, requires a reduction in the starting dose for patients with a homozygous mutation, as these patients have higher exposure to the active metabolite of irinotecan than heterozygous patients. This genetic polymorphism can be used to identify patients that are likely to experience serious toxicity and adjust their dose accordingly (8,9). Biomarkers can provide the ability to identify potential toxicity before clinical symptoms develop, and aid in monitoring toxicity that may develop into an irreversible toxicity before it is diagnosed.

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indication, the use of biomarkers can provide information early on to indicate if the patient population may be responsive to therapy.

BIOMARKERS AND SURROGATE MARKERS

A biomarker differs from a surrogate marker from a regulatory viewpoint, thus, biomarkers and surrogates markers have different roles in the drug approval process. A surrogate marker, or endpoint, may substitute for a clinical endpoint and reduce the time necessary to demonstrate clinical effectiveness, allowing approval and market entry earlier than the use of a clinical endpoint. A biomarker demonstrates biological activity and cannot substitute for a clinical endpoint. For clinical trials for interferons used to treat Hepatitis C, the biomarker neopterin serves as an indication of immune system activation. For interferon alfa (Intron A®, Schering), the biomarker serum alanine aminotransferase (ALT) serves as a measurement of liver function. Effect on viral replication through the measurement of the level of virus (early viral load reduction), however, is an indicator of an effective treatment, and thus, serves as a surrogate endpoint.

Filgrastim (Neupogen®, Amgen) stimulates the survival, proliferation, differentiation and function of neutrophil precursors and mature neutrophils. The biomarker of 'absolute neutrophil count' is a measurement of biological activity, while 'duration of sustained neutropenia' is a surrogate marker reflective of the clinical endpoint 'incidence of febrile neutropenia' in patients receiving chemotherapy or myeloablative therapy, followed by bone marrow transplantation.

DEVELOPMENT AND VALIDATION OF A BIOMARKER

Biomarkers must be validated from a clinical and scientific point of view. Selection begins with a hypothesis related to biological plausibility. This then leads to identification, animal studies, and methods for establishing clinical relationships via trials and concepts of test-retest reliability and predictive power. This validation should take into consideration the design of preclinical and clinical studies. Depending on the level of acceptance of a biomarker in the medical community, this could be a time-consuming task. In general, the more novel the target, the more time and effort is required to validate a clinical biomarker. Biomarker development should begin simultaneously to and proceed in parallel with the drug development programme (10).

Biomarkers must have the ability to be measured in an analytical system with well-established performance characteristics and evidence that links to the physiologic, toxicologic, pharmacologic or clinical significance of the test result. Analytical methods must be developed to quantitate the biological response. Validation is required to confirm accuracy, reliability, consistency and precision of the assay.

CONCLUSION

Biomarkers reduce risk, expedite the development process, increase the success rate of clinical trials, and support expanded labelling into broader patient populations. Biomarkers that have been accepted by the medical and scientific community can be readily adopted into clinical trial design. Novel biomarkers require development and validation simultaneous to the development of the biopharmaceutical. For each step of the biopharmaceutical development programme, biomarkers add value and aid decision making. ◆

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