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The Essential Components of a Credible Biomarker Strategy Plan for Your Drug Development Candidate

By Rajesh Krishna

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One fundamental tenant of pharmacology is understanding how a drug works. One can glean over product package inserts to the mechanism of action section to see how the approved drug works for its approved indication. Designing the right experiment or set of experiments is crucial for understanding the mechanism of action for novel entities. In some cases, this is poorly defined, in which case the package insert lacks information on drug mechanisms. See the inset below for one well researched drug, hydroxychloroquine:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rheumatoid Arthritis, Systemic Lupus Erythematosus and Chronic Discoid Lupus Erythematosus

The mechanisms underlying the anti-inflammatory and immunomodulatory effects of PLAQUENIL in the treatment of rheumatoid arthritis, chronic discoid lupus erythematosus and systemic lupus erythematosus are not fully known.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/009768s053lbl.pdf

On the other hand, the mechanism of action of the immuno-oncology drug, durvalumab, is well described in its package insert. Valuable information on the biomarkers and surrogate endpoints are clearly delineated. See the inset below.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Expression of programmed cell death ligand-1 (PD-L1) can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production. Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody dependent cell mediated cytotoxicity (ADCC). PD-L1 blockade with durvalumab led to increased T-cell activation in vitro and decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models.

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf

The durvalumab mechanism of action is particularly interesting from a scientific point of view in that there are not only tumor level data shown but also how the hypothesis of increased T-cell activation was assessed.

The use of biomarkers is key to understanding drug mechanisms. While biomarkers can play a crucial role in drug labels, this white paper will explain why the inclusion and assessment of biomarkers within drug development can also inform many decisions.

Let's explore the use and necessity of biomarkers.

The National Institutes of Health defines a biomarker as a characteristic that is measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention (Littman and Krishna, 2011). For use in certain situations, for example within regulatory contexts, biomarkers must be validated or qualified, which is characterizing a biomarker to demonstrate its fit for purpose. They can be different types, most described by the disease pathway sequence. More proximal biomarkers are target engagement biomarkers. More distal biomarkers may be better characterized as mechanism-based biomarkers (Wagner, 2002). Their use, whether proximal or distal, transcends the drug discovery and development continuum. They could be used in pathfinding, research, development, and applications. They add value to the drug developer because this centralized all-in-one tool can help inform how a drug works, determine the right dose, optimize the patient population, and assist in persuading a regulator how the biomarker effect can yield clinically important benefits (Figure 1). Therefore, biomarker selection is a valuable opportunity not worth missing!

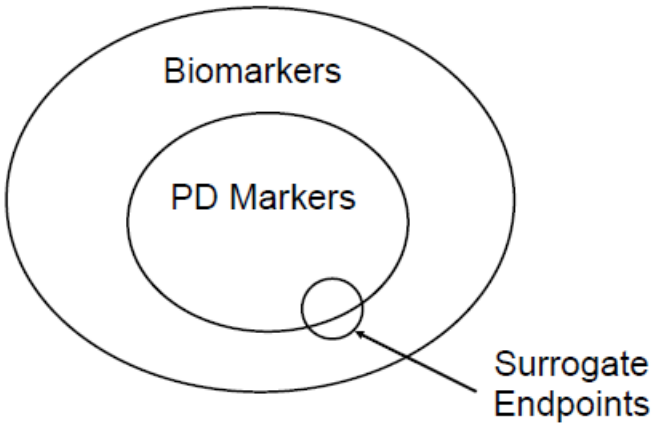
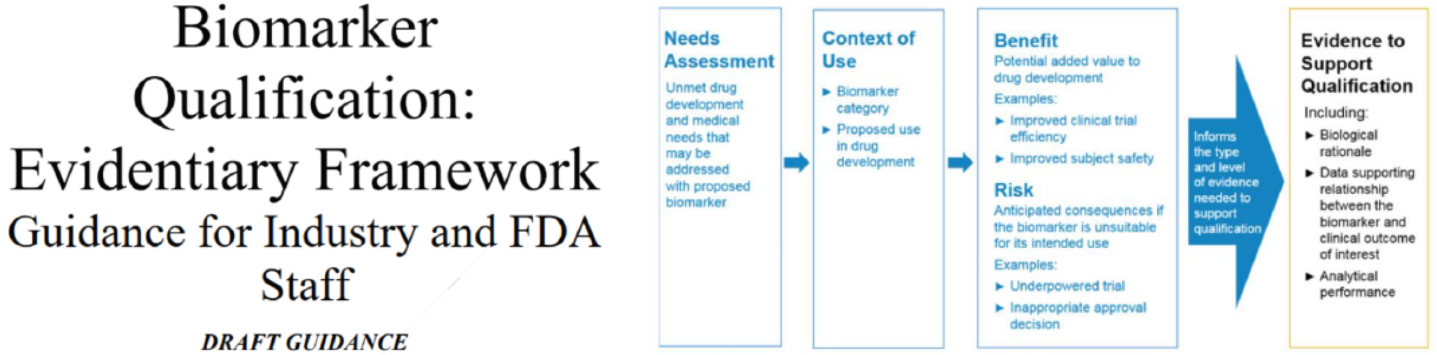


Figure 1.

The relationship between biomarkers and surrogate endpoints
(Adapted from Wagner, 2002).

According to Wagner, 2002, a putative biomarker may be involved in the disease pathophysiology, could be related, but not directly involved in disease pathophysiology, or not involved in the disease pathophysiology. Based on these considerations, biomarkers could be used to assess the probability of technical and regulatory success for novel developmental candidates. A pharmacodynamic (PD) marker refers to a biomarker of pharmacologic response whereas a clinical endpoint quantifies a characteristic related to how a patient feels, functions, or survives. A surrogate endpoint is a biomarker that substitutes for a clinical endpoint. In Wagner's perspective, both PD markers and surrogate endpoints are subsets of biomarkers.

To ensure biomarkers are credibly used and applied in regulatory contexts, the drug developer can refer to regulatory guidances.



There is a whole array of regulatory applications of surrogate endpoints. The FDA has a dedicated page devoted to drug approvals based on surrogate endpoints. Here is a snapshot of those approvals.

Adult Surrogate Endpoint Table

Disease or Use	Patient Population	Surrogate Endpoint	Type of approval appropriate for	Drug mechanism of action
Alpha-1-antitrypsin deficiency	Patients with congenital alpha-1 antitrypsin deficiency	Plasma alpha-1 proteinase inhibitor	Traditional	Alpha-1 protease inhibitor augmentation
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum Insulin-like growth factor-I (IGF-1)	Traditional	Growth hormone receptor antagonist
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum growth hormone and serum insulin-like growth factor-I (IGF-1)	Traditional	Somatostatin analog
Acute Bronchospasm	Patients with acute bronchospasm associated with reversible obstructive airway disease or exercise	Forced expiratory volume in 1 second (FEV1)	Traditional	Beta-2 adrenergic agonist
Anthrax vaccine	Persons at high risk of exposure to anthrax	Anti-protective antigen antibody response	Traditional	Induction of immunity

Source: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

Let's reflect on the choice of these biomarkers within drug development.

Key consideration 1: Biomarker best practices in drug discovery and development

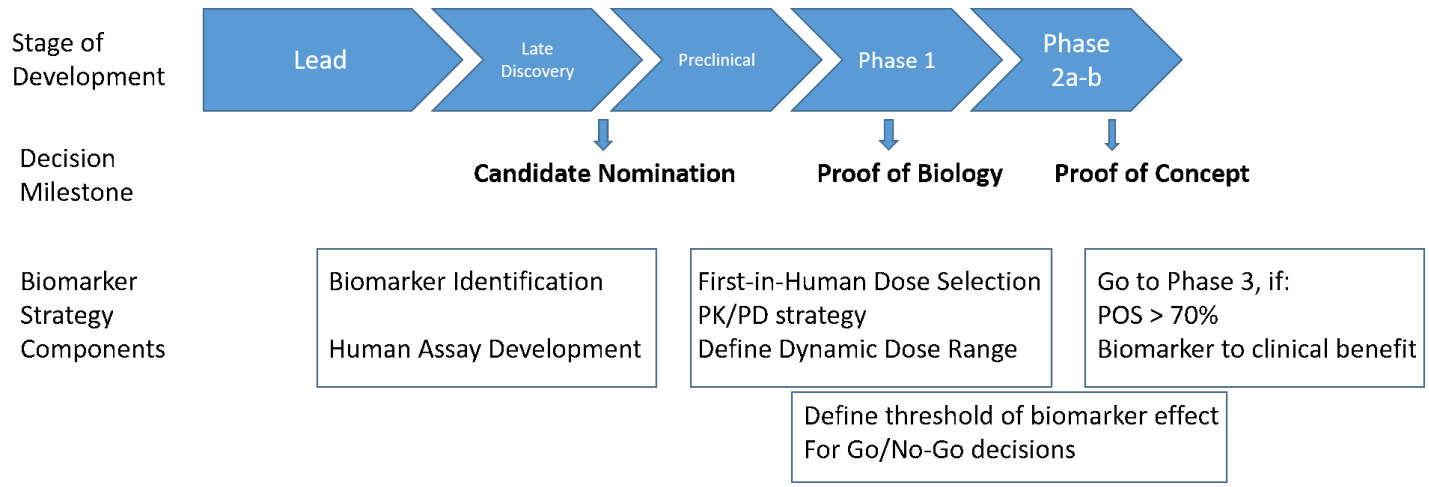
Biomarkers can be set up for decision making as activities are starting to develop for phase 3 clinical trials. In essence, such biomarkers can support internal decision making to understand the probability of success, in yielding a dose at which there is sufficient probability to exceed the effective concentrations required or associated with a certain pharmacological effect. In the early development phase, stakeholders need to consider three key decisions:

- Identifying the best candidate for further development
- Showing proof of biology using a battery of disease pathway biomarkers, and
- Defining proof of concept.

One might have some trepidation to understand the magnitude of effect in small phase 1 studies. However, precision analytical tools allow drug developers to identify the probability of seeing a defined effect using model-informed drug development capabilities. The role of each of these decision components and their sequencing is shown in Figure 2.

Figure 2.

The biomarker continuum within early translational development



An example of how this fits in drug development is the work of Jones et al., 2021 in the translational development of savolitinib, a potent inhibitor of the mesenchymal epithelial transition (MET) factor receptor tyrosine kinase. Jones et al developed a pharmacokinetic/pharmacodynamic (PK/PD) model to relate the inhibition of MET phosphorylation (pMET) by savolitinib with anti-tumor activity. Their chosen translational biomarker was MET phosphorylation, their target engagement biomarker. The anti-tumor activity is an example of a distal biomarker. The authors rationalize that extensive (>90%) and prolonged inhibition of pMET is necessary for observing meaningful anti-tumor activity. Using these relationships, they determine the effective concentrations at 50%, namely an EC_{50} of 0.38 ng/mL. This is a good example where a biomarker such as pMET was used to support dose selection in a first-in-human study but also determine the threshold effect size expected using pMET.

Key consideration 2: Use of biomarkers to interrogate a scientific hypothesis

Biomarkers can also help determine whether a target is worth pursuing. This is perhaps the most underutilized benefit of biomarker science. Take, for example, the story of leukotriene B4 receptor antagonists. Leukotriene B4 (LTB4) is a potent lipid mediator of inflammation that is said to have derived from arachidonic acid through the 5-lipoxygenase (5-LO), 5-LO-activating protein, and leukotriene A4 hydrolase enzymes. LTB4 was hypothesized to mediate multiple biological functions through its interaction with two distinct receptors, LTB4 receptor 1 (BLT1) and LTB4 receptor 2 (BLT2). Based on the known data showing high concentrations of LTB4 in tissues from patients with inflammatory disease, several companies started their drug hunting efforts by developing potent antagonists of this receptor (e.g., CP 195543- Pfizer, CGS 25019C - Novartis, ONO 4057- Ono, LY 293111- Lilly, and BIIL 284- Boehringer Ingelheim; clinicaltrials.gov). Promising levels of efficacy were then seen in multiple animal models including many inflammatory pathways such as arthritis, multiple sclerosis, asthma, and psoriasis. Compound after compound showed reductions in inflammatory cell infiltration in experimental medicine models of LTB4 skin challenge or BAL fluid neutrophils. However, as these molecules were taken into phase 2 trials, they showed no significant efficacy in predominantly inflammatory diseases such as rheumatoid arthritis, colitis, asthma, and psoriasis.

There are many inherent challenges in this hypothesis. It might have been possible that a plethora of early LTB4 antagonists were not selective to BLT1 or 2, or that the role of BLT2 in LTB4 signaling and inflammation was not unequivocal. One could envision that the rational choice of biomarkers and understanding the quantitative threshold that best correlated with efficacy could have mitigated against the high failure rate in these diseases. In an insightful commentary, Bhatt et al suggest that the complex self-regulating system that LTB4 plays a role in promoting inflammation may have been the reason for a high failure rate with this target.

Key consideration 3: Identifying a “do-not-exceed” threshold

While most biomarkers set up a minimum threshold for which it is expected to exceed to claim a certain biological benefit, biomarkers can also be used to set up “do not exceed” limits. As you may have guessed, such limits are imposed to mitigate safety issues. This is mostly for the drug developer since there has been a tendency to look for high doses so that no efficacy “is left on the table” for competitive reasons or efficacy reasons.

A very good highlight of such limits comes from the dopamine D2 receptor occupancy database, which predicts short-term clinical response, extrapyramidal side effects including akathisia (the inability to remain still), and hyperprolactinemia associated with certain anti-psychotic drugs. As you can tell from Figure 3, the “do not exceed” receptor occupancy is approximately 78%.

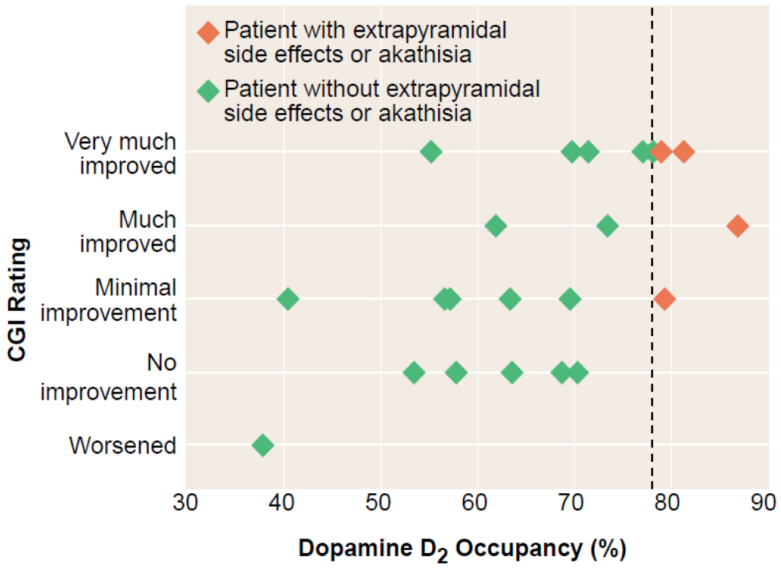


Figure 3.

Relationship between anti-psychotic side-effects (Clinical Global Impression "CGI Rating" and their D2 receptor occupancy (Adapted from Kapur et al., 2000).

Drug developers targeting the development of a novel antipsychotic can benefit from such intuitive and simplified relationships to carve out a receptor occupancy domain that would yield desirable levels of efficacy but at acceptable safety.

There are several benefits of the rational inclusion of biomarkers and surrogate endpoints within a drug development programs. Their inclusions should be prudent and consistent with their use in hypothesis generating experiments.

The FDA offers the following guidance in selecting surrogate endpoints in clinical trials (https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development).

- Is there reliable and consistent epidemiologic evidence supporting the link between the endpoint and clinical benefit?
- How strong is the correlation between the endpoint and the clinical outcome?
- Has the endpoint been shown to predict a clinical benefit with a different drug?

In summary, having a credible biomarker is key to understand how the drug works and can help with designing and assessing pharmacological properties of the drug. In early phases, they can aid in the selection of the dose and its dynamic range. Biomarkers with relationships to outcomes can help with decision making on dose to be selected or to indicate to investors or management that continued funding would help advance the molecule in question. The steps of biomarker identification and rational use starts in the preclinical phase and continues throughout the product lifecycle. Evolution of biomarkers to surrogate endpoints requires well controlled clinical trials but has benefits for the overall program, including being the basis of the accelerated approval pathways.

For more information on how Certara can help you select and apply biomarkers within the drug development spectrum, contact us.

About the Author

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Rajesh Krishna, PhD is a Senior Director in Integrated Drug Development at Certara Strategic Consulting. Rajesh came to Certara after a rich 20+ years of pharmaceutical industry experience in translational and clinical development at Merck, Sanofi (legacy Aventis), and Bristol-Myers Squibb. He has contributed to 40+ INDs, more than 200 Phase 1/1b studies; and to the worldwide registration of 9 new molecular entities.

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