Worldwide Clinical Trials

Clinical Drug Development at the Crossroads: One Drug, Multiple Indications

Portfolio Review and Strategic Decision Processing

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Introduction:

Optimal strategic decision-making in the development stage of a novel drug requires moving beyond the innovation associated with a product's mechanism of action. This perspective impacts a range of domains impacting a decision affecting an optimal clinical development plan, including competitive environment, trial designs, time to key inflection points, regulatory pathways, and the overall potential for adoption and access.

When a firm is developing a novel investigative product (IP) based on its effect on a particular molecular target or on its effect on a particular biomarker—rather than on its effect on a specific indication—there comes a point at which that developer needs to make decisions about directing and prioritizing its efforts. Such an IP may have a measurable effect on multiple indications sharing a common molecular target or biomarker, which would make it a "platform" therapy. However, creating products targeting each of these indications concurrently is not a practical business strategy for most developers. Such efforts would be expensive, require the execution and management of a complex array of clinical and non-clinical trials, and involve extensive engagement with regulators — likely in multiple therapeutic areas.

Given several potential paths for development, an innovator must determine where best to target its efforts. Many obvious factors can inform such a decision, including scientific rationale, the size of the population affected, precedent studies that might influence program design, the existence of current enabling non-clinical data, the financial runway available to a developer, and the potential income to be generated by successfully marketing a new therapy. But these are not the only factors a developer may want to consider. Other factors might include the degree of competition within the development community, the characteristics of patient subtypes affected by an indication, the existence of regulatory guidance and the dynamics of the regulatory pathways in different regions (FDA vs. EMA), as well as the positions and priorities of patient advocacy groups, payers, and potential investors (just to name a few).

To make well-informed strategic decisions about how best to focus potentially divergent development efforts, decision-makers need insight into all these matters. This is where a strategic portfolio review can play an important role in a development program. Such a review involves a thorough analysis of the opportunities and challenges associated with the different paths a developer might consider taking. The insights arising from a portfolio review can empower decision-makers both to prioritize effectively and to navigate near- and long-term development challenges with greater clarity.

Dissecting a portfolio review

A portfolio review examines a range of topics — in detail, and from the perspectives of different stakeholders — for each clinical indication that a developer might be considering, based on the known biological or pharmacological properties of the IP:

Rationale

Given the intended therapy; is the concept clinically and scientifically intriguing, with directly monitorable effects?

Drug Discovery Paradigms

What options exist to facilitate development (*in vitro, in vivo, ex vivo, in silico*)? Are there analytically- or clinically-validated PD/biomarkers that would enable early signals of target engagement? Do these biomarkers have potential clinical utility and translation into practice?

Trial Designs

Are designs, endpoints, durations and methods of analysis predictable? Is there an easy translation between non-clinical and clinical investigations that would support predictability?

Regulatory Pathways

Does formal regulatory guidance exist to address all aspects of clinical development? Are there opportunities for accelerated, breakthrough, or other abbreviated pathways?

Competitive Landscape

Are there other competing clinical development efforts underway — domestically or internationally that might not only affect access to appropriately qualified patients but also to appropriately qualified centers and staff?

Adoption and Access

Using the US as a model, are there significant barriers to patient access? Can cost drivers be identified? Can they be preemptively incorporated into program design? Are there opportunities for a parallel development effort to build and validate the value proposition for the agent that will later inform formulary placement and reimbursement efforts?

A portfolio review examines each of these topic areas in detail, and the findings can be expressed both qualitatively and quantitatively. A qualitative estimate frequently requires consultation with individuals possessing both drug discovery and drug development expertise, particularly in the area of translational medicine. For a quantitative estimate, one can score the strength of each answer on a Likert scale and the sum of the individual scores becomes the total score for each indication being reviewed. By comparing the qualitative and quantitative scores, both on an individual and summary basis across indications, decision-makers can better understand why certain indications might prove more strategically attractive than others.

Practicalities of a portfolio review

The input variables for a portfolio review arise from many different sources. This includes data developed externally to the project at hand — on a similar indication or a similar mechanism of action (MOA) — as well as data developed internally through the normal course of a drug development campaign. Some data sources may be elusive. For example, a small or mid-sized developer may have little or no experience navigating the FDA's regulatory pathways (let alone any experience navigating the regulatory pathways that exist outside of the United States), creating a blind spot that will prove problematic for developers trying to make informed development decisions. It is worth noting that this problem becomes exacerbated when potential indications exist within different therapeutic areas, where the regulatory review processes and points of emphasis may be markedly different.

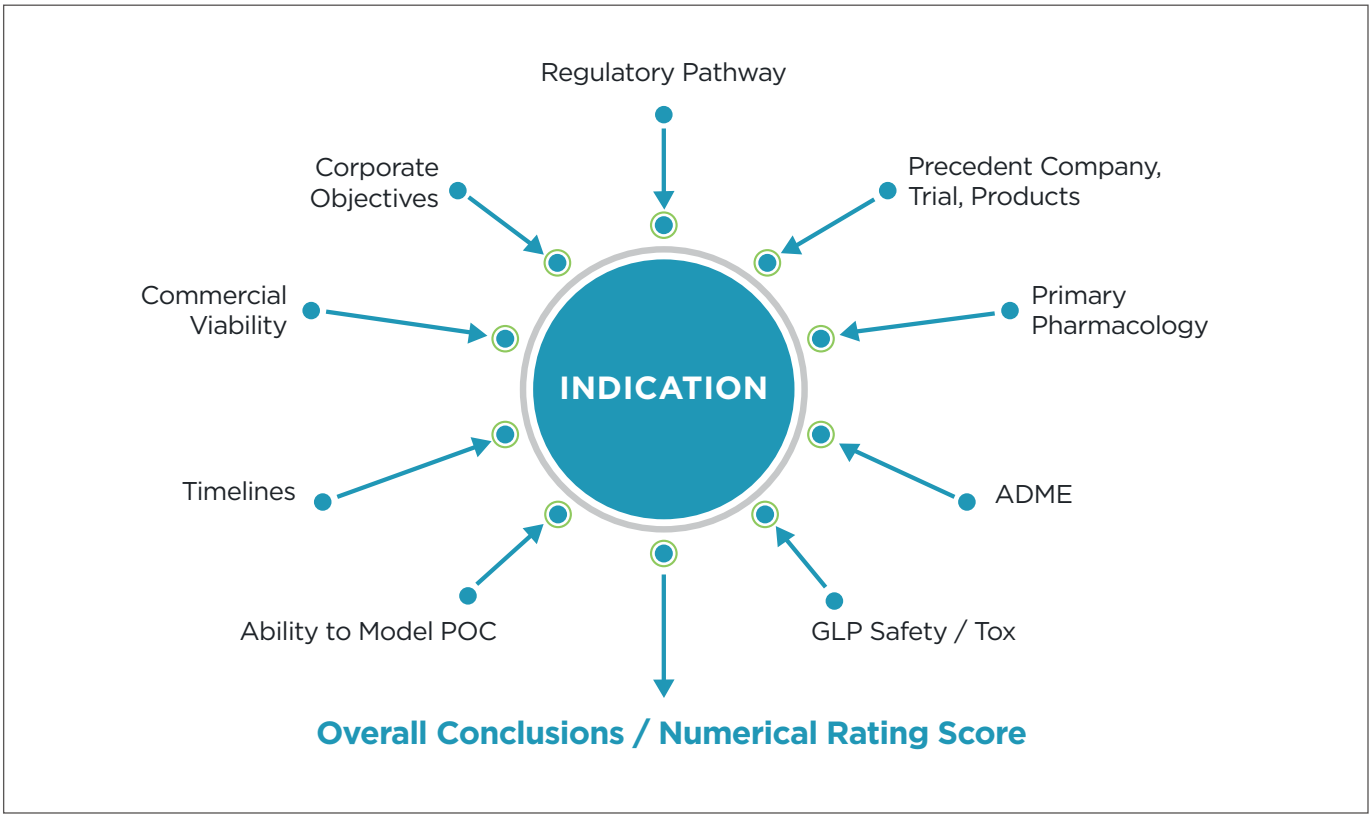

Figure 1: A portfolio review considers a range of factors and yields a quantification that can facilitate strategic decision making

Insights into the kind of regulatory reception the IP might encounter when coupled to one indication or an alternative will most likely arrive through consultation with a strategic partner who is familiar with the various regulatory pathways in place. The same is true when it comes to reviewing other companies, trials, and products competing in the same space. Business decision-makers who monitor the news and daily industry reports may have some insight into the competitive environment, but these press releases and information released to the general public will not yield the site-level details that decision-makers need at this juncture. Those details are more likely to be surfaced by a thorough search of targeted public and private databases and journals, which can yield information about the state of any clinical trials or biomarker studies that may be underway for each indication. No organization other than a CRO would be privy to the highly granular, site-specific information that will dictate whether or not a program of research is feasible, or timely engaged.

This research can also provide insight into patient populations, which are initially somewhat different than those populations that would ultimately receive the product. This is due to the nature of the drug development process, in which exposure to the IP moves from highly leveraged patient samples and sites to more generalized patients and sites as development proceeds. This research also provides insight into procedures, patient interest in study participation and rates of retention, and the feasibility of conducting different design adaptations of clinical trials in the future. It can provide a developer with insights into the kinds of endpoints that have previously been used across indications and phases of development. Congruency in endpoints and durations can provide a base of comparison across studies that will prove advantageous later in the development program.

Additional analyses can identify existing products (or products that are known to be within the discovery space) that have been approved or targeted for use in each indication and can identify the strengths and shortcomings of those products, based upon available data. This analysis may identify opportunities for "piggybacking" assessments on top of a registration program to acquire additional information on healthcare utilization that could be relevant to key stakeholders and that could drive patient access and payer formulary placement. All this information becomes particularly relevant as a sponsor compares the therapeutic qualities, characteristics, and revenues associated with existing products — or products in development — to the therapeutic qualities, characteristics, and revenues it hopes to recoup from its efforts if it proceeds with further development in this space.

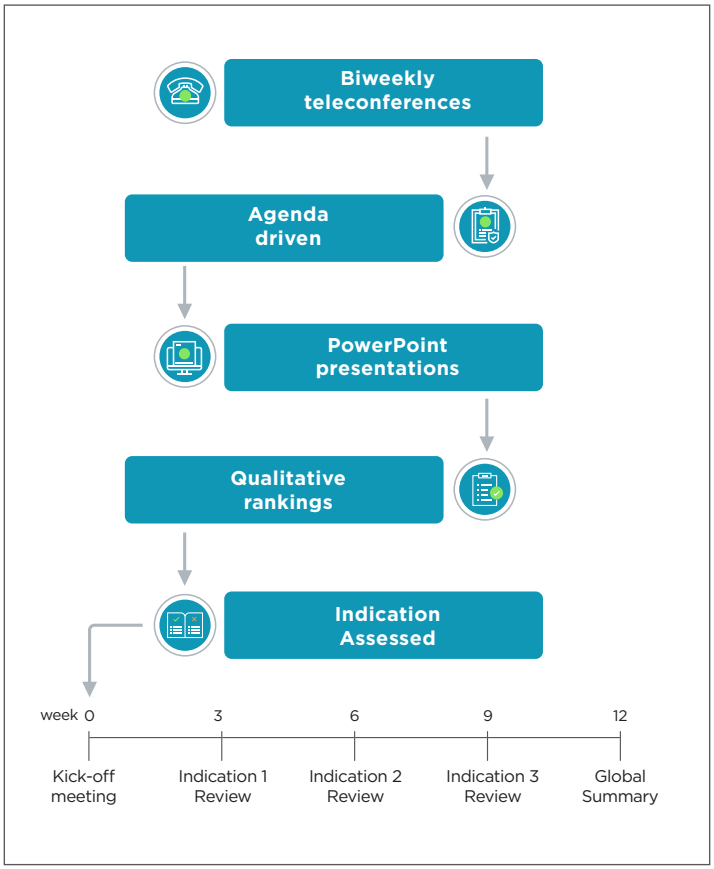

Figure 2: A portfolio review typically focuses on as many as three indications. A multi-domain assessment of each indication takes approximately 15 business days, for a total engagement period lasting between 8 and 12 weeks

A portfolio of options, some of them not obvious

Portfolio reviews in general are indication agnostic, however, their utility is exemplified in oncology where investigational products are unique, patient phenotypes are highly nuanced, and innovative trial designs, such as basket programs enrolling many tumor types, are often used for collecting initial safety and preliminary efficacy data. The impetus for portfolio review in these circumstances occurs when multiple individual indications appear intriguing yet no significant differences in efficacy, safety, or other parameters that would otherwise dictate development and commercial success suggest a singularly compelling path forward. Indeed, providing a rationale for an indication has generally proven to be the least challenging element within the review process. Rather, it is the ability to anticipate and weigh other elements in program design that frequently cause pause.

For example, a firm with a novel chemotherapeutic product found itself at a developmental crossroad. Its product could in principle address unmet clinical needs in four different cancer types, including subdivisions that are clinically acknowledged to be relevant to drug development. As many as 13 separate indications existed as candidate clinical targets. Yet, a multivariate approach was required to correctly integrate and adjudicate different perspectives regarding overall clinical and commercial viability of each of those phenotypes. A portfolio review performed on four of these indications (including localized, locally advanced, and metastatic disease subtypes within each of the four indications of interest) revealed a mosaic of options that previously had not been considered.

As a consequence of this comprehensive review, the organization developed a revised business stratagem that encompassed multiple indications. It also produced a new clinical development plan that prioritized development by indication, time constraints, financial constraints, and likelihood of adoption by physicians and formulary placement by payers.

Facilitating data-based decisions

At this point, a developer considering a portfolio review might legitimately ask about the potential for a portfolio review to complicate rather than streamline business decision-making. A portfolio review may present a sponsor with myriad options that were not previously known to exist, which can introduce a level of uncertainty about the best paths forward rather than providing the clarification and guidance that a portfolio review should provide. When performed properly, though, a portfolio review provides a sponsor with a portfolio of ranked options and data-based insights into how best to leverage each option appropriately. It takes into consideration internal organization strengths and dynamics, the demands of key stakeholders, the complexities of different regulatory pathways, and the variety of routes that exist for moving an IP towards a commercial debut.

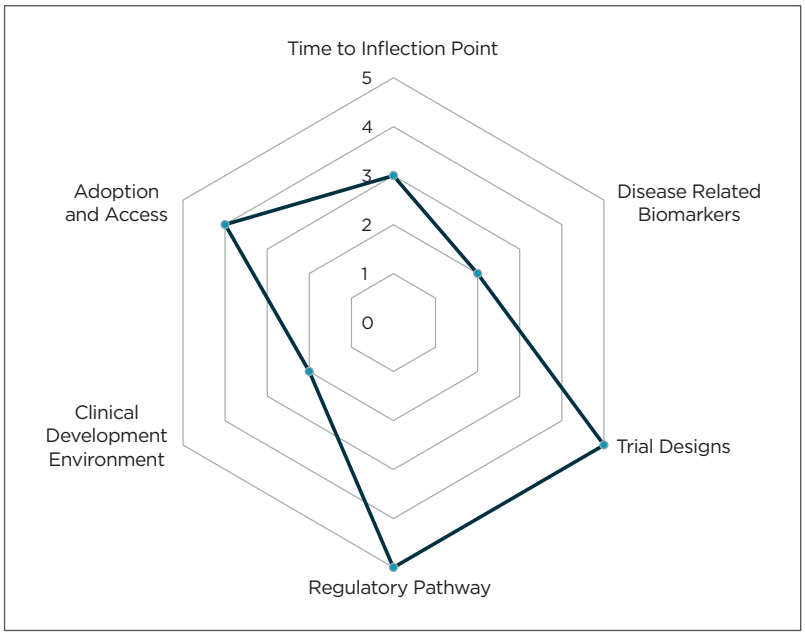

Figure 6: One can quantify the result of each analysis on a Likert scale. By comparing scores across indications, decision-makers can better understand why certain indications might prove more strategically attractive than others.

Delivering the insights needed to move forward on a sound footing

It doesn't matter if the decision-makers instigating a portfolio review are scientists, operations specialists, or experts in business development: data is crucial to all decision making. A comprehensive portfolio review needs to satisfy the questions of many stakeholders. It must provide detailed, evidence-based insights backed by decades of clinical understanding—all in an easily-digestible format.

Ultimately, a portfolio review should not be a simple regurgitation of known data, but a thoughtful analysis and interpretation of the known data and more. When conducted by a partner experienced in working with a wide range of businesses, clinical and scientific subject matter experts, patient advocates, regulatory agencies and other external stakeholders, a comprehensive portfolio review can provide new insights into ways a developer can better assess the attributes and liabilities associated with each potential target and development path.

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