How to Optimize Personalized Medicine R&D and Commercialization Decision-Making

Sean Xinghua Hu, Ph.D., M.B.A.[1,2,3,4,*] and Edward Abrahams, Ph.D.[5]

A growing number of personalized medicine (PM) therapeutics (*1–4*) are impacting clinical practice today, while pharmaceutical companies are expanding their commitment (*5*) to PM approaches in new drug development. However, despite success stories such as trastuzumab, imatinib, panitumumab, and crizotinib, the development and commercialization of PM remain highly challenging and fraught with obstacles.

Many of the challenges facing pharmaceutical companies are external, such as those related to regulatory approval, market access/reimbursement, and physician and patient education. Many others are internal, relating to operational and technical, or organizational and strategic issues.

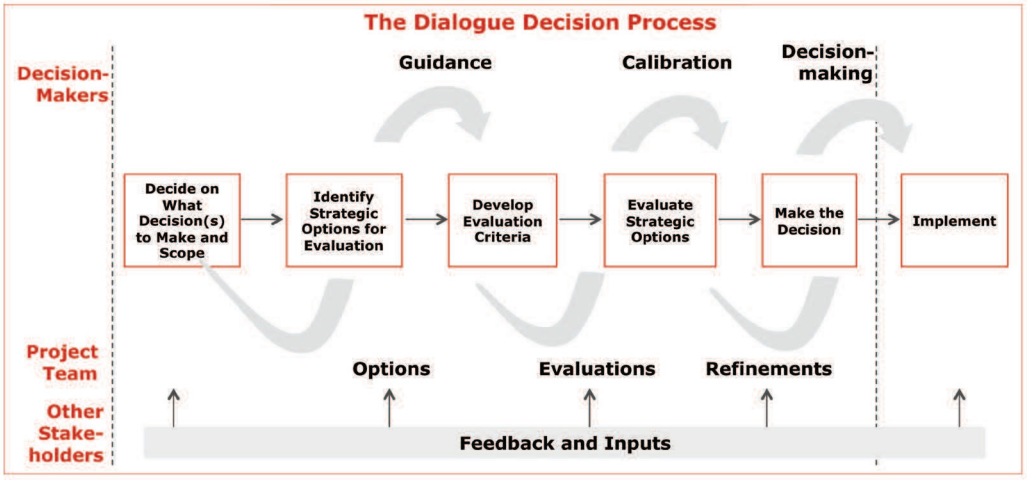

Figure 1. The "Dialogue Decision Process" (*8*). The project team engages decision-makers and other stakeholders within an organization to establish shared ownership, alignment, and fact-based decision-making to effectively achieve consensus.

The Personalized Medicine Coalition (www.personalizedmedicinecoalition.org), an educational and advocacy organization based in Washington, D.C., representing scientists, patients, providers, and payers, has been addressing many of the external challenges.

This article focuses on the critical internal challenges for pharmaceutical companies when optimizing the decision-making process for PM strategies, particularly for mid- to late-stage drug candidates faced with "big bets" investment decisions. Here the term "personalized medicine" refers to "stratified medicine" (*6,7*)—drugs intended for patient subpopulations stratified via companion diagnostic tests.

THE CHALLENGE OF COMPLEXITY AND UNCERTAINTY

Aside from the common challenges facing conventional drug development and commercialization, there are even more challenges in the context of PM, including greater complexity and uncertainties with respect to scientific and clinical validation, regulation, reimbursement, and the economics of targeting smaller patient populations.

More specifically, the financial value of a potential PM consideration can be affected by many factors, such as biomarker prevalence, negative and positive predictive values of the companion diagnostic test, and the impact on a drug's profile by stratifying patients. It is further complicated by the uncertain and countervailing nature of those variables, such as the possibility of securing a higher segment market share within a smaller patient population.

To address the challenge, the product teams need to develop and apply ***in-depth personalized medicine-specific knowledge*** and focus on the many scientific, clinical, commercial, and operational factors in order to make clearer decisions in PM development, for example:

Scientific and Clinical: Are there choices for biomarkers, such as drug-specific biomarkers [e.g., C-C chemokine receptor type 5 (CCR5) tropism test for maraviroc] versus drug-class biomarkers [e.g., epidermal growth factor receptor (EGFR) for cetuximab and panitumumab]; or binary/dichotic biomarkers [e.g., v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation] versus continuous biomarkers (e.g., protein expression/immunohistochemistry tests)?

- How would each choice affect biomarker prevalence and addressable patient size?
- How would the availability, level of technical complexity, and pricing and reimbursement status of a companion diagnostic impact physician adoption of the drug, and eventually the drug's adoption and market share?
- How would the use of a companion diagnostic influence patient treatment adherence?

Commercial and Operational: How would the drug's performance in the targeted population affect its competitive differentiation, and eventually, market share?

- How would patient stratification and comparative effectiveness impact the drug's pricing and reimbursement?
- How would the need to co-develop a companion diagnostics affect drug clinical trials, regulatory review, and launch?

[1]Head, Bionest USA & Managing Director, North America, BIONEST Partners, New York, NY, USA
[2]Designated Representative of the Personalized Medicine Coalition, Washington, DC, USA
[3]Adjunct Professor, Chinese National Human Genome Center at Shanghai, Chinese Academy of Sciences, Shanghai, China
[4]Visiting Professor and Senior Advisor, Beijing Genomics Institute (BGI), Shenzhen, China
[5]President, Personalized Medicine Coalition, Washington, DC, USA
*Corresponding Author: shu@bionest.com

- How would the adoption of a personalized medicine strategy impact the drug's sales force operations and marketing strategies after launch?

One can further address the complexity and uncertainties of PM strategy decision-making by committing to a more ***robust analytical approach:***

- Use probabilistic financial modeling and simulation instead of single-point deterministic modeling, allowing for better assessment of the combined impact of individual modeling variable uncertainties.
- Analyze the sensitivity of the uncertain variables for their impact on the drug value, so as to determine the relative priority of the variables and inform risk mitigation measures.
- Seek to reduce the uncertainties of input variables in the financial model via appropriate market research.
- Best estimate the probability of technical and regulatory success based on industry benchmarks and product/disease area-specific features.

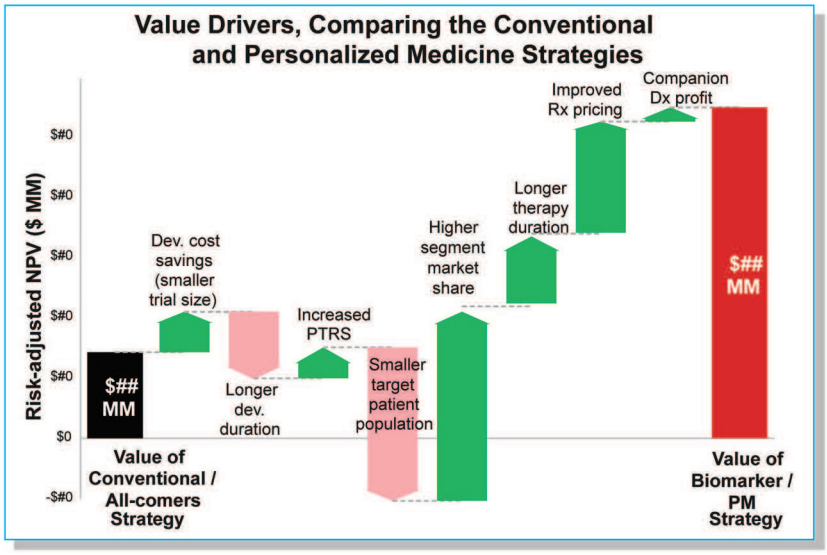

Figure 2. The PM "Waterfall Chart." This details the drivers of value comparing the net present value (NPV) of the conventional all-comers vs. biomarker-based personalized medicine (PM) development and their corresponding commercialization strategies. Note that other product-dependent value impact factors may also be applicable under other PM situations, such as impact on underserved patient segment, compliance, and persistency. PTRS, probability of technical and regulatory success.

THE CHALLENGE OF CONCENSUS BUILDING

Beyond market analytical considerations, there is also a key corporate sociological component of PM strategy decisions. Within the corporate environment there remains uncertainty about the new PM approach, sometimes leading to premature dismissal of the PM strategy without sufficient analysis of the options. Given the many challenges of PM, pharmaceutical colleagues often are less than fully committed to those strategies.

To better address this corporate sociological component and more effectively build consensus in PM strategy decision-making, companies need to refine their overall drug research and development (R&D) and commercialization processes to fully integrate PM and companion diagnostic elements by answering such questions as what PM and companion diagnostics-specific key decisions need to be made, when, by whom, and how? Typical R&D processes usually define key stage gates (or decision points) along the drug value chain, objectives at each stage, responsibilities and accountability, activities, and resource assignment. A systematic and integrated PM process will ensure that the right PM strategy decisions are made at the right time, and based on proper analysis of the facts instead of biased views.

In making decisions on PM strategy issues at a specific decision point in the overall R&D process, a dialogue-based subprocess can be employed to enhance the effectiveness of decision-making and consensus building. As illustrated in Figure 1, the ***Dialogue Decision Process*** engages both decision-makers and internal stakeholders to create shared "ownership" of the issues at hand, and align analysis with the aim and scope of decisions to be made. As a result, this dialogue process creates an opportunity to build broader alignment within the organization, which is especially important when introducing a new paradigm for drug development.

Aside from an optimal decision process, clarity of communication using ***effective reporting tools*** is yet another key to obtaining buy-in and consensus for PM strategies throughout the organization. One example of such tools, as illustrated by the "Waterfall Chart" (Figure 2), compares conventional and PM development/commercialization strategies, and quantifies the contribution of variables to the commercial net present value (NPV) of a drug. The visual representation of an otherwise complex analysis provides transparency, and a platform for constructive, evidence-based debate towards consensus.

CONCLUSION

Optimal decision-making for PM R&D and commercialization, to a certain extent, is an art requiring a large degree of prognostication. It benefits from a combination of intelligent modeling based on the collection of market evidence and observations, and the "soft" art of bringing people together to make informed decisions through a cloud of complexity and uncertainties. By basing models on a probabilistic understanding of uncertainties and sensitivities to different variables, and by structuring the decision-making process to be more rigorous, inclusive, and committed to PM, one can ensure that product development consensus will converge on the optimal path.

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