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Full length Article

Economic viability of Stratified Medicine concepts: An investor perspective on drivers and conditions that favour using Stratified Medicine approaches in a cost-contained healthcare environment

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ABSTRACT

Rationale: Stratified Medicine (SM) is becoming a natural result of advances in biomedical science and a promising path for the innovation-based biopharmaceutical industry to create new investment opportunities. While the use of biomarkers to improve R&D efficiency and productivity is very much acknowledged by industry, much work remains to be done to understand the drivers and conditions that favour using a stratified approach to create economically viable products and to justify the investment in SM interventions as a stratification option.
Concept: In this paper we apply a decision analytical methodology to address the economic attractiveness of different SM development options in a cost-contained healthcare environment. For this purpose, a hypothetical business case in the oncology market has been developed considering four feasible development scenarios.
Conclusions: The article outlines the effects of development time and time to peak sales as key economic value drivers influencing profitability of SM interventions under specific conditions. If regulatory and reimbursement challenges can be solved, decreasing development time and enhancing early market penetration would most directly improve the economic attractiveness of SM interventions. Appropriate tailoring of highly differentiated patient subgroups is the prerequisite to leverage potential efficiency gains in the R&D process. Also, offering a better targeted and hence ultimately more cost-effective therapy at reimbursable prices will facilitate time to market access and allow increasing market share gains within the targeted populations.

Introduction

As advances in science give the rise to increasingly precise tools for the diagnosis and treatment of disease, Stratified Medicine (SM) becomes a natural result of biomedical science and a promising path for the innovation-based biopharmaceutical industry to create new investment opportunities [1]. SM has the potential to improve medical outcomes for patients and economic outcomes for the healthcare system. Matching therapies to specific patient subpopulations using clinical biomarker/diagnostic-based SM offers the prospect of enhancing patient care with more effective and safe drugs, delivered with a greater probability of treatment success [2]. For industry, the SM approach provides an opportunity to improve efficiency and productivity in the research and development (R&D) process and to demonstrate a differential therapeutic profile to be successful and rewarding in an increasingly competitive and cost-contained market environment. There have been several examples where SM has created clinical success and achieved accelerated product approvals, particularly in oncology (Glivec®, Herceptin®, Xalkori® and Zelboraf®) which have triggered increased investments in biomarker-based R&D by the industry in recent years[3] However, the implementation and adoption of targeted therapies have been slower than many proponents have hoped or predicted, indicating possible concerns from investors about the economic viability of such approaches [4].

While the use of biomarkers to improve R&D efficiency and productivity is very much acknowledged by the industry, less is understood about the drivers and conditions that favour using a stratified approach to create economic viable products and to justify the investment in SM interventions as a stratification option. The commercial impact of using a diagnostic-guided

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strategy must be considered carefully in direct relation with patient access and benefits. Arguments over segmenting the market, and hence the loss of potential revenues, will be weighed against possible accelerated market and patient access with increasing market share gains within the target sub-population or faster market adoption [5]. Investigating and understanding of certain scenarios is critical for industry as several factors throughout drug development, reimbursement and market adoption affect the potential clinical and commercial success of a stratified medicine approach.

The differential therapeutic profile of SM could allow for more economic viable applications by addressing numerous offsetting factors which will influence investment decisions within the pharmaceutical and diagnostics industries. The objective of this paper is to explore these factors by developing a straightforward economic analysis for SM comparing different strategic options to help decision making for future R&D investments in an increasingly cost-contained healthcare environment. For this purpose, several case studies will be addressed.

Economic viability of stratified medicine

Pre-approval economic considerations

There is anticipation that SM not only provides better value for money, thanks to improving drug effectiveness and reducing toxicity, but could also help to reduce R&D costs. Notably, diagnostic testing may enhance the efficiency of clinical trials of new compounds and allow smaller and cheaper studies, still adequately statistically powered. This may occur if diagnostic testing information can identify a subgroup of patients most likely to respond to a given treatment and early enough reduce clinical trials sizes such that the drug development process can indeed become more efficient. Smaller and possibly shorter clinical trials are likely to reduce drug development costs and perhaps may allow earlier commercialisation of targeted therapies [6]. However, it is equally plausible that project specific investments in discovery and validation of biomarkers and diagnostic tests will involve additional costs and complexity to the inherently risky drug development process. Sometimes, the use of stratified clinical trial populations will involve comprehensive biomarker evaluation and validation steps, including an appropriate biomarker assay development in order to identify and test predictive biomarkers. Also, more narrowly defined inclusion criteria may lead to lengthier recruiting, the need for additional sites and higher costs.

Hence, since SM is in its early stages, it has been indicated that potential efficiency gains in R&D may only result in the long term [7]. In addition, from an economic perspective, a more targeted patient population may lead to smaller groups of eligible patients while R&D and other investment to bring products to market remain similar or even increase. In this case, premium prices seem inevitable and difficult discussions with reimbursement authorities emerge. Also, faster adoption or longer effective patent life for an SM intervention could be argued to offset the reduction in potential revenues from patient stratification. Yet SM may not only diminish groups of eligible patients, it can also enlarge them by redefining the disease space at the molecular level and across traditional disease boundaries (e.g. targeting solid tumours in oncology may be used for various cancer types) [8] or by extension of the target indication (move from 3rd line to 2nd or even 1st line) due to an increased cost-benefit ratio. All in all, if superior clinical performance is adequately evidenced, actual revenues might increase because SM enjoys faster and wider adoption [9].

In addition, diagnostic testing may improve a company's abilities to better identify promising drug candidates (assets) leading to higher probability of success of R&D projects due to lower attrition rates in the R&D portfolio and lower sunk costs of failed R&D projects. In particular, it has been shown that reducing phase II and III attrition is the strongest lever for improving R&D efficiency and reducing the costs per New Molecular Entity (NME) [10]. However, a significantly leverage of this impact on R&D budgets will require a certain number of targeted therapies with improved cost-benefit ratios as part of the company's development portfolio [11].

Time to product approval and commercialisation

The "time to market" is a key factor influencing the economic profile of a new compound and future cash-flows, which determine the economic value of a product. If an SM approach can shorten development time because diagnostic testing has streamlined the clinical trial programme, cash inflows will be shifted to earlier time periods, increasing the net present value of this compound. In addition, a compound reaching the market earlier can leverage longer periods of patent protections, which also increase expected economic returns [6]. Zelboraf® (vemurafenib) and Xalkori® (crizotinib) both achieved accelerated approvals (both approved by FDA in August 2011) and demonstrated that targeting can significantly shorten development time and cost [12,13]. Zelboraf® is used to target melanoma patients together with its companion diagnostic (BRAF gene mutation test) and reached the market within 4.5 years, including a regulatory approval time of 3.6 months, through an expedited process. Xalkori®, was developed for the treatment of patients with non-small cell lung cancer (NSCLC) with a specific alteration in the ALK gene. The drug together with its ALK FISH probe companion diagnostic reached the market within 5 years from start of Phase I trials. Here, Pfizer used a stratified approach to establish clinical outcomes (i.e., safety and effectiveness) for the target populations involving only 255 patients. The approval process for the drug and its associated test took only 4.9 months, well ahead of standard review times for priority drugs [14].

Therapeutic effects and biomarker features

Prospective stratification is difficult and may also not always be feasible as scientific and clinical factors place some limits on the pace of development. In certain therapeutic areas, understanding of the molecular basis of diseases is insufficient to select biomarkers at early stage of development [15]. In addition, common disease conditions are often influenced by multiple genes/biomarkers in ways not always well understood in early development stages. In other therapeutic areas, there is no immediate medical need for diagnostic-based therapies. Gaining knowledge about the molecular mechanisms of diseases and the underlying common molecular pathways of how a drug interferes with next-generation genomic technologies is crucial for drug development before clinical symptoms and outcomes are studied in clinical trials [16]. Hence, predictive biomarkers can often be applied rather late in the clinical development programme, when clinical data show that an optimal benefit-risk profile is only achieved in a subpopulation of patients [8]. However, a decision of whether or not to continue clinical development, either with or without diagnostics, should ideally be made no later than at the end of Phase II [17] to allow for more efficient trial designs with smaller patient populations. Trusheim et al. [18] see three key factors when assessing therapeutic areas and biomarker features to drive economic value for stratified medicines compared to empirical medicines: the therapeutic effect with the selected population, the prevalence of the predictive biomarker and the clinical performance of the companion diagnostics (ability to distinguish treatment responders from non-responders).