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Innovative oncology products: time to revisit the strategy development?

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Trends for global population growth, ageing and an increasingly sedentary lifestyle are leading to a rise in a number of diseases with high mortality rates including cancer.[1] An inevitable consequence of this is increased healthcare costs, in particular for oncology. According to a recently published report, spending on all medicines used in the treatment of cancer patients worldwide reached nearly US$150 billion in 2018, with two-digit growth as compared with the previous year.[2] There is, therefore, a crucial need to develop innovative medicinal products (InMP) to provide oncology patients with better treatment alternatives at potentially lower cost. One way to do this is to design more effective strategies for the development and commercialisation of InMP that integrate from the outset the needs of patients, healthcare professionals (HCPs) and medical societies, regulatory authorities and a variety of other stakeholders.

Strategy serves as a road map for InMP from the earliest stages of development through to market authorisation and beyond. Three archetypes of strategy (corporate, business and operational) are typically used by an organisation to determine the most effective manner to achieve specific goals and objectives.[3] Corporate strategy outlines where a company will compete in terms of the industrial segments and/or specific markets they plan to enter and win. Business strategy details the actions required to gain a competitive advantage and is often referred to as product strategy. Operational strategy defines the day-to-day guidance needed to deliver corporate and business strategies.[3] While all three are relevant to the pharmaceutical industry, development and commercialisation of an innovative medicine is mainly driven by product-specific strategy and is the focus of this editorial. Product-specific strategies are generally developed by cross-functional multidisciplinary teams; however, it is not uncommon that clinical development, whose objective is to demonstrate positive risk/benefits for obtaining marketing authorisation, becomes uncoupled from the postapproval activities. An integrated strategy is, therefore, required that includes and synergises both preapproval and postapproval activities.

There is very limited published research dedicated to product strategy development and its implementation in the pharmaceutical segment in general and in oncology in particular. Most strategic concepts and tools, for example, Porter's Five Forces, Curry's Pyramid and Kotler's 4P's (Product, Price, Promotion and Place) of marketing,[4–6] have been adopted from non-pharmaceutical industries, such as Fast Moving Consumer Goods or the automobile industry. Frequently, those frameworks are either not directly applicable or require adaptation to be of value in the pharmaceutical segment. For example, product strategies in the non-pharmaceutical industry are typically customer centric, identifying customer or end-consumer needs and working backwards to the technology during development and after product commercial launch. In contrast, the end-consumer of a pharmaceutical product (the patient) has less influence on preapproval product strategy development and less decision powers in postapproval commercialisation as compared with regulatory and health technology assessment agencies, HCPs, payers, medical insurers and other decision makers. This paper will present the arguments for why the reverse approach, starting with an in-depth understanding of product attributes, its implications for the required clinical outcomes, and then designing the integrated InMP strategy, is more appropriate in the pharmaceutical space based on a number of factors, unique to the pharmaceutical environment.

First, pharmaceutical research & development is a complex, costly, risky and time-consuming process involving numerous stages with multiple risk factors.[7 8] This is particularly the case in oncology where across all

trial phases, the average duration of an oncology trial in 2018 was 3.2 years compared with 1.8 years for all other therapy areas, a difference of over 40%.[9] As a result, the therapeutic products reach the market with 12–13 years or less of patent protection since the first synthesis of the new active substance.[8] Even the introduction of breakthrough therapy designation by the U.S. Food and Drug Administration (FDA)[10] or priority medicine designation by the European Medicines Agency (EMA)[11] to expedite the review of investigational products intended to treat serious or life-threatening diseases, may not be sufficient to influence dramatically the overall time of product development. The selection of appropriate and clinically relevant outcomes is essential for pivotal registration trials in oncology and is one of the most critical factors influencing its duration and probability of success at regulatory review and approval. Overall survival (OS) is a frequent primary endpoint in oncology trials, but as treatment options continue to prolong life, newer oncology therapies must now demonstrate benefit in patient populations that are living longer than before.[12] While challenging, there is significant value in integrating predictive biomarker development alongside the InMP to identify the patients who are most likely to be responders and thus to provide targeted therapies.

Second, the discovery, development, manufacture and commercialisation of an InMP has no guaranteed profitability. The median cost of developing a single cancer drug has recently been estimated at US$648.0 million.[13] However, during the development process, many potential InMPs fail to demonstrate clinically relevant outcomes or are associated with serious side effects. They may, therefore, never reach or succeed in the pivotal phase III clinical trials required for market authorisation.[9] This large upfront outlay and considerable uncertainty in the InMP development process mean that a very high return must be sought by investors and shareholders to compensate for the risks. As a result, list prices of new cancer drugs at launch have risen steadily over the past decade. The median annual cost of a new cancer drug launched in 2018 was US$149 000, compared with US$79 000 for those launched in 2013. The recent FDA approval of two chimeric antigen receptor T-cell therapies tisagenlecleucel and axicabtagene ciloleucel was for two of the most expensive anticancer therapies ever.[14]

Third, the pharmaceutical industry is increasingly subject to scrutiny over safety, efficacy and costs, particularly in oncology where the increasing prevalence of cancer is coupled with a high expenditure on new drug development. Continued innovations in oncology focus primarily on improving overall or progression-free survival as efficacy endpoints. However, these innovations may also be accompanied by significantly higher development costs, as well as side effects and toxicities.

Fourth, the pharmaceutical industry also differs from other industries in the separation of decision makers, payers, prescribers and end-consumers (the patients). Thus, regulatory and/or health authorities evaluate product-specific data to authorise entry to the market (including pricing and reimbursement); physicians make treatment decisions assisted by the clinical guidelines and consensus recommendations; insurance companies (government or private) assess the products for inclusion in the reimbursement and co-payment lists; and the patient is the final end-consumer who might have a voice in the form of patient groups, although with limited influence on InMP evaluation, approval and finally prescription. This is in contrast to many other industrial segments (such as information technology, automobile, etc.) where the end-consumer is both the payer and decision maker. In those segments, the most successful product strategies therefore and mainly built on differentiation and competitive advantage: offering customers/end-consumers the value that competitors do not have.[15]

In countries where health technology assessment is in place, this is relied on by payers, pricing and reimbursement agencies to provide information on the risks and benefits of new treatments compared with available options, support price negotiation and determine reimbursement status and medical insurance coverage schemes. Integrated InMP strategies that address these issues upfront and incorporate OS, progression-free survival and patient-reported outcomes into pivotal registration trials, most likely will provide the required evidences in a timely and efficient manner. This should include early postapproval studies with a focus on comparisons with available treatment regimens that differ in efficacy, toxicity and intensity. A consideration of the above factors that are unique to the pharmaceutical industry must be taken into account for successful strategy development of an InMP.

To date, very limited published research is available on product strategy development and its implementation in the pharmaceutical segment and in oncology in particular. A search of the literature on Google Scholar, PubMed, Bielefeld Academic Search Engine and Academia.edu using the search terms: ‘product strategy’, ‘product strategy development’, ‘medicinal product’, ‘new product’, ‘oncology’, ‘innovative’ and ‘prescribed product/medicines’ identified very few publications addressing strategy development for an InMP, and those that did all highlighted the pivotal role of clinically relevant product attributes. In oncology, one paper was identified that examined value demonstration to healthcare. Studies focusing on product-specific attributes, such as OS, progression-free survival, adverse events as well as population size, and trial comparator were regarded as key.[16] In cystic fibrosis, the strategy developed for the innovative product ivacaftor was to continue to expand label indications so that more patients with different mutations could benefit from this MP.[17] A third article focused on the failure of Bristol Myers Squibb to adequately market the innovative technology responsible for the benefits

of Glucovance (a glibenclamide/metformin single-pill combination for the treatment of type 2 diabetes): modified versions of glibenclamide and metformin, specialised drug release, ability to take with meals.[18] No publications were identified that specifically addressed InMP strategy development in oncology, for example, the role of the end-consumer versus product attributes.

While patients are an important part of the pharmaceutical product development process with the ultimate goal being to help them combat their disease, they have less influence on decision process and purchasing/negotiation as compared with end-consumers in other (non-pharmaceutical) industries and less influence on product strategy development. Instead, it is a deep knowledge of clinically relevant product attributes (structure, function, biological activities, clinical safety and efficacy) that largely influence and shape the product development programme and integrated InMP strategy. These attributes are the foundation to meet unmet therapeutic needs and therefore benefit the patient as end-consumer, but during the development process the patient and his/her needs as decision-maker will have little influence on InMP strategy, especially prior to marketing authorisation and availability.

A prime example of the importance of product attributes in InMP development is provided by the path to approval of the first-in-class, immune checkpoint inhibitor, ipilimumab. The role of cytotoxic T-lymphocyte antigen-4 blockade was first reported in 1996,[19] but it was not until 2011 that ipilimumab received its first approval for the treatment of patients with unresectable or metastatic melanoma. One of the major hurdles was the initial use of traditional chemotherapy-based response assumptions in the trial design. When the primary endpoint was changed, although late in the trial, to OS, subsequent data showed a significant benefit in favour of ipilimumab.[20] In retrospect, ipilimumab would have benefited if one of the currently recommended clinical frameworks, such as the European Society for Clinical Oncology (ESMO) Magnitude of Clinical Benefits Scale (MCBS), had been available at the time of phase III trial design. Their requirement for OS as a primary endpoint would have helped to reduce the time from drug discovery to market authorisation. This example serves to illustrate that an understanding of a product's unique attributes, such as mode of action and expected therapeutic effect, is required early to be integrated in the strategy. As many oncology InMP may benefit from expedited approval pathways, the time for additional data collection and launch preparation is at a premium.

To further support observations that clinically relevant product attributes are at the core of InMP integrated strategy development, a pilot LinkedIn survey of pharmaceutical industry representatives was performed.[21] Participants were asked which of the following attribute(s) they believed was the most pivotal when developing a successful product strategy:

1. Knowledge of product characteristics (structure, function and biological activities).
2. Product clinical evidence/data (efficacy, safety and superiority vs already available products).
3. Knowledge/understanding of the end-consumer (target patients) needs.
4. End-consumer (target patients) decision power, including product's purchase.
5. Effective communication channels to reach out directly to end-consumers/patients.

Attributes were rated on a 5-point scale from 1 not important/not sure to 5 extremely important. The results showed that 70% of responders rated product characteristics as extremely important. Knowledge of target patients' needs was rated very important by 50% of participants and extremely important by 30%. End-consumer decision power and effective communication channels were regarded as less important. While this pilot survey is limited by its open source and small sample size, it supports the hypothesis that optimal strategy development in the pharmaceutical industry should have the product at its centre. The survey findings also highlight the need to revisit pharmaceutical product strategy development and to place more emphasis on product-specific and clinically relevant attributes, such as safety and efficacy. For example, if a treatment demonstrates good results, these will be rapidly shared on social media, and this has become an increasingly important channel for reaching physicians and engaging them about therapies. This was confirmed by the official hashtag of the 2018 American Society of Clinical Oncology (ASCO) annual meeting, which generated 90 309 tweets over the 5-day meeting from over 20 000 unique authors, with 500 million potential impressions, mainly on product-specific clinical outcomes.

The findings from the survey are very much aligned with the value-based healthcare concepts that have been adopted by key international medical societies in oncology. A number of organisations have developed frameworks to assess the value of an oncology regimen based on measures related to treatment, supporting data and cost including: the ESMO MCBS, ASCO value framework (VF)[22] and the National Comprehensive Cancer Network (NCCN) evidence blocks.[23 24] These clinically oriented scales and frameworks define value as health outcomes that can benefit survival, quality of life, symptomatic relief or even avoidance of toxicity, and therefore, should be considered at the earliest time of InMP integrated strategy development as they anticipate HCP and patients' needs and payer constraints. It is noteworthy that individual patient disease characteristics and patient-reported outcomes and satisfaction are not considered by any of these scales and frameworks (table 1), which rely instead on clinical efficacy and safety parameters.[22–25]

A recent analysis found good agreement between the ASCO VF and ESMO MCBS[26] thereby allowing stakeholders to appraise therapies based on their value in a transparent and objective manner. Consistent clinically relevant data throughout the clinical programme combined with strategies to individualise treatment, for

Table 1 Factors influencing the ASCO, NCCN and ESMO value frameworks (adapted from Slomiany et al, 2017[25]).

Endpoints	ASCO VF	NCCN evidence blocks	ESMO MCBS
Primary endpoints			
Efficacy	Advanced disease, HR (death), OS, PFS, response rate	Variable, dependent on indication	Advanced disease, OS, PFS, palliation of symptoms, response rate
Safety/toxicity	Based on side effect frequency, grade	Effect on daily life	Grade 3/4, severe side effects
Secondary endpoints			
Treatment-free interval	✓	✗	✗
Tail of the curve	✓	✗	✗
Quality of life/palliation	✓	✗	✓
Patient preferences	✗	✗	✗
Cost			
Drug costs	Advanced disease: drug acquisition cost/month Adjuvant therapy: drug acquisition costs/ entire treatment regimen	Total treatment cost	Not specified, left to payers to evaluate
Cost to healthcare system	✗	✓	✗

ASCO, American Society of Clinical Oncology; ESMO, European Society for Clinical Oncology; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival.

example, by the identification of biomarkers to better predict treatment response, will improve the value of treatment for patients and reduce development resources.

SUMMARY

Pharmaceutical product strategy development differs compared with other industries. One of the key differences is that it is the clinically relevant product attributes that are pivotal to a successful InMP. It is therefore essential that pharmaceutical companies build a durable integrated product strategy to provide a solid evidence base for more effective differentiation from available therapeutic alternatives. This should include implementation of available clinical benefit scales and frameworks along with patient-reported outcomes from an early stage of integrated InMP strategy development.

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