Pharmaceutical and Medical Products Practice

Value-driven drug development—unlocking the value of your pipeline

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Pharmaceutical companies do not need reminding that drug development has become more difficult: even safe and effective drugs struggle to gain regulatory approval and market access. A new paradigm, whereby R&D and commercial teams collaborate at the beginning of Phase 2 to keep a laser-like focus on stakeholder value, can transform performance.

By Valentina Sartori, Michael Steinmann, Matthias Evers, and Petra Jantzer

In the 1990s, pharmaceutical companies could bank on a successful drug launch if they could prove that the drug was safe and effective. But the goal posts have shifted. Regulators want proof that new drugs are safer and more effective than those already on the market,[1] and even regulatory approval is no guarantee of success. Health care providers the world over are struggling with rocketing costs, which means they are reluctant to pay for drugs that do not deliver significant incremental benefits to patients—particularly if they come with a high price tag.

The result is that many drugs fail to gain broad market access or to earn the developers an acceptable rate of return. Between 1998 and 2008 for example, the UK's NICE granted restricted or no market access to almost 60 percent of drugs from the top ten pharmaceutical companies. Meanwhile, since its inception in 2004, Germany's IQWiG has classified 70 percent of the drugs it has reviewed as "benefit not proven".

The market access challenge is likely only to increase as payors demand ever more value for their money to contain health care costs, which have risen twice as fast as GDP since 1970. Accordingly, pharmaceutical companies have experimented to try to improve their odds of success. Some, like GSK and Novartis, have worked closely with payors in late-stage development; others, like Pfizer and Janssen, have done so post launch, for example through risk-sharing agreements. In our opinion, however, the only way pharmaceutical companies can consistently launch successful drugs is by working to meet the market's needs much earlier in the development process.

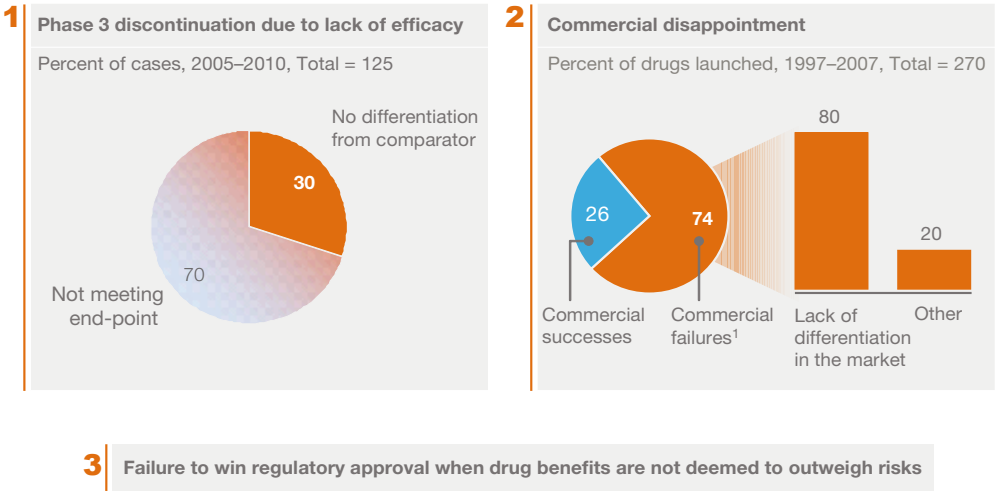
This requires a new paradigm. R&D and commercial teams need to start working together when planning for proof of concept (PoC) in Phase 2. And rather than searching for a gap in the market for the compounds they develop, these cross-functional teams need to design a compound to fill a market gap. That gap will be defined not just by the needs of patients, but also by those of regulators, Health Technology Assessment bodies (HTAs), and payors.

Successful drugs will be those that demonstrate their value to all these stakeholders and do so early in development. This new paradigm is what we call "value-driven drug development." It seeks to maximize the value of a company's current pipeline and replenish it with new and valuable compounds by steering research in the right direction. In so doing, it helps mitigate three of the main risks in drug development: discontinuation in Phase 3 due to lack of efficacy; commercial disappointment—often because of lack of differentiation; and failure to gain regulatory approval because the compound's risks are deemed not to outweigh its benefits (Exhibit 1).

[1] The FDA's tougher scrutiny of data in non-inferiority trials is an example of this. See report GAO-10-798 for further details.

Value-driven drug development helps mitigate three key risks

Exhibit 1



1 Commercial failure defined as NPV at launch less than average cost of development
SOURCE: Pharmaprojects, APM Health Europe, Evaluate, McKinsey analyses

The four imperatives of value-driven drug development

Value-driven drug development has four essential components.

1. Understand what outcomes matter to patients and other stakeholders at least five years before launch

Even five years before launch, the patient is in focus. At this stage, the task is to identify, based on real-world evidence, patient needs not yet met by competitors for specific indications, and understand what profile a new compound should have to satisfy those needs. The search then continues to identify a sub-set of patients who might benefit most from the compound, perhaps because certain genetic variations respond well to it. True, segmentation in this manner necessarily restricts the size of the market for the proposed drug. Importantly, though, it accentuates the potential differentiation from competitors' compounds.

One example of a successful drug that has been narrowly targeted in this manner is Roche's Herceptin. The drug specifically targets the 25 percent of breast cancer patients whose cancer is related to an over-expression of the gene factor HER2. Oncology is the area in which most personalized medicine research has been conducted to date, but we believe other therapeutic areas are suitable too.

Efforts to differentiate a compound and so demonstrate its value can go further still by clearly defining different components of the overall outcome that the sub-group of patients would most value. For example, beyond its efficacy, the compound might also improve a dialysis patient's quality of life by reducing the number of hospital visits required.

The focus then turns to other health care stakeholders who influence registration and reimbursement decisions—that is, governments, regulators, HTAs, and payors.

Stakeholders' assessments of a new drug's value will differ, as will the data they require to demonstrate its value. Regulators, for example, are mainly concerned about the risks and benefits compared with the standard of care, and mostly require randomized control trials and "hard" clinical end-points directly related to the progression of the disease. Payors care about the total cost impact on their patient population, while HTAs want to know whether the incremental benefits of a new drug can justify its costs. For that, HTAs might require observational and experimental studies demonstrating a more subjective assessment by physicians or patients of the drug's impact on symptoms or quality of life. Regulators and payors are aware that their different demands can be hard for pharmaceutical companies to accommodate, and some have started to collaborate to try to reach more common ground (see sidebar, "Greater Collaboration").

The development team will also need to understand each stakeholder's relative influence. Although it used to be physicians who ultimately decided whether or not a drug was prescribed, payors and HTAs increasingly hold sway. That said, stakeholders' influence varies by geography. HTAs have little influence over reimbursement decisions in the United States, for example. That is the remit of the insurance companies. But in Europe, HTAs influence important pricing and reimbursement decisions. For example, NICE rejected the use of Genentech's cancer drug Avastin in two cancer indications (metastatic colorectal cancer and first-line treatment for metastatic renal cell carcinoma) on cost grounds, resulting in sales worth just €10 million in the United Kingdom in 2008. That compared with sales of €300 million in France, where no HTA assessment was made.

Development teams will also need to find an approach that satisfies the two main regulatory agencies in the United States and Europe. It is becoming increasingly difficult to submit one registration package that works for both. For example, the EMA always requires a pediatric plan. The FDA does not. The EMA always requires a comparator for oncology drugs. The FDA does not. Their assessments differ too. The FDA approved Wyeth's anti-depressant drug Pristiq, while the European regulator had concerns about differentiation, prompting Wyeth to withdraw its submission.

Armed with insights into patients' needs, competitors' strategies, and stakeholders' expectations, development teams are in a position to consider their options strategically. The target product profile (TPP) sought is one that will be clearly differentiated from the future standard of care—that is, at the time of launch; one that delivers maximum value to stakeholders; and one that carries an acceptable risk profile in terms of development risk.

2. Sharpen the focus of Phase 2 to define value as well as dose

Today, having assessed the compound's safety in Phase 1, Phase 2 usually focuses on understanding the efficacy of the compound (Phase 2a), then the right dose (Phase 2b). A few companies, such as Novartis and Wyeth, have started to do things differently, trying to make the development process more seamless.[2] Our approach is marked by the manner in which Phase 2 homes in as early as possible on where value might lie.

[2] Novartis's approach is known as Delphi. Wyeth's is known as Learn and Confirm.

First, Phase 2 is used to identify the sub-set of patients who have the optimal risk-benefit profile for the compound, as described earlier. Astra Zeneca recently received European approval for all lines of therapy for its lung cancer drug Iressa for a sub-set of patients with a specific biomarker—but only after withdrawing its first EMA submission following a non-conclusive Phase 3 study that targeted the full population of patients, then conducting a new, more targeted study. Its experience underscores the potential benefits of early patient stratification and the use of biomarkers in clinics.

Second, besides testing efficacy and dosing, Phase 2 is used to start testing the additional questions likely to be raised in Phase 3 by stakeholders seeking value. In this way, the development team can identify early on those compounds unlikely to meet stakeholders' needs, stop development, and avoid further wasted costs. Meanwhile, those that remain in development have a better chance of gaining regulatory approval and market access.

Interacting with payors, HTAs and/or advisory boards at this stage will help test the development team's initial hypothesis about where value lies. Their input will shed light on what a new compound might have to deliver to be judged better than the standard of care; which end-points need to be proven; and the data required. Comparative studies that give an early sense of how the compound differs from the standard of care and how the pivotal Phase 3 study may need to be refined accordingly are also useful. Designing Phase 3 trials to test the compound against the likely future standard of care rather than a placebo is another means of reinforcing the compound's value.

Third, whenever possible, clinical trials in Phase 2 should be designed to optimize costs, time, and data quality but without sacrificing ethical standards. Take as an example a compound addressing a well-known mechanism already validated. Time and costs will be saved by using an adaptive design that combines Phase 2a (proof of efficacy) with 2b (dose ranging), thereby reducing start-up times and improving dose-response estimates. Interim results can be analyzed and modeling and simulation techniques used to understand the dose-response curve before continuing the trial and further refining the pharmacodynamic model.

Greater Collaboration

At the end of 2010, the EMA launched a pilot project with health care stakeholders from six European countries (France, Germany, Italy, the Netherlands, Switzerland, and the United Kingdom) to assess the therapeutic and economic value of new drugs at an early stage of development, and share their views with pharmaceutical companies. Astra Zeneca, GlaxoSmithKline, and Johnson & Johnson are involved in the pilot, with the focus currently on drugs to treat Type 2 diabetes and breast cancer.

Since the beginning of this year, the EMA has also been collaborating with the European Network for Health Technology Assessment to understand how risk/benefit data contained in European Public Assessment Reports for centrally authorized drugs can be used in HTA assessments.

Regulators and HTAs are also collaborating at the national level. In the United Kingdom, NICE and the Medicines and Healthcare Products Regulatory Agency initiated a pilot program last year for pharmaceutical companies to receive parallel and independent scientific advice from both bodies on how to design drug development programs that would suit both agencies. There have been no participants in the program to date—something NICE puts down to the strict application criteria—but many companies have expressed an interest.

In Sweden, the Dental and Pharmaceutical Benefits Agency and the Medical Products Agency also offer joint advice to companies that request it. Since 2009, there have been 20 such joint assessments.

If the trial fails to demonstrate that the drug is sufficiently differentiated, the compound can be dropped knowing limited resources have been wasted. On the other hand, should the compound show promise, Phase 3 will be reached more quickly. A good example of innovation in the design of a clinical trial, enabling a speedy trial and ultimately faster registration, was Novartis's development of Ilaris, a treatment for Muckle Well's disease. Novartis used modeling and simulation techniques to select the dose range, which was then confirmed in a seamless Phase 2b/3 trial.[3]

Fourth, when entering Phase 2, teams need a development strategy for a mechanism of action (MoA) that addresses more than one indication. Even before PoC, a plan is needed that maximizes a drug's potential value, taking into account all the possible indications and respective patient segments. Different indications are likely to have different value profiles. They will meet unmet needs to a greater or lesser extent, carry different risks, require more or less time to develop, be priced differently, and have different interdependencies—for example, a study for one indication may reveal valuable lessons for another. All this needs to be assessed in order to understand how best to stagger development.

3. Upgrade team and leadership capabilities

Value-driven drug-development teams require a particular blend of skills and capabilities, as do the governance bodies that oversee them.

The team

Drug development has tended to be the turf of clinicians. But if stakeholder value is the goal, other specialists need to be part of the team too.

Even at the research phase, translational science experts should be present to identify possible biomarkers and develop a biomarker strategy to help patient segmentation. Then, in Phase 1, molecular diagnostics specialists should help develop companion diagnostics to measure in clinics the biomarkers identified. Strategic marketers also have a role, ensuring that market insights, such as what competitors are up to, how other MoAs in development might compete for success, and how the market will have evolved by the time of launch, are incorporated into the development strategy.

When planning for PoC at Phase 2, still more skills will be required. The strategic-access function seeks to understand where value lies for payors and HTAs. It then works with clinicians to define the data required to satisfy hard and soft end-points, comparators, and differentiation requirements. Modeling and simulation will bring in the necessary mathematical skills not only for PKPD modeling but also for full drug-to-disease modeling or for decision-analysis support.

[3] See J. Orloff, F. Douglas, J. Pinheiro, S. Levinson, M. Branson, P. Chaturvedi, E. Ette, P. Gallo, G. Hirsch, C. Mehta et al, "The Future of Drug Development: Advancing Clinical Trial Design," *Nature Reviews Drug Discovery* 8, 949-957 (2009), doi: 10.1038/ndr3025 Perspectives.

The team leader

Traditionally, the leader of a development team is a clinician who has little contact with marketing or commercial divisions. To promote a value-driven culture and operate effectively within it, however, the compound in development will need its own CEO—someone who will be able to manage a cross-functional team, aggregate its members' input, and keep a balance between clinical excellence and successful commercialization. Drug-development experience, project- and team-management skills, and strategic-thinking ability will all be required.

In addition, the team leader will need to establish strong knowledge networks with internal and external stakeholders and key opinion leaders in order to stay abreast of research developments, monitor competitors, and be able to react to changing circumstances.

The governing body

A similar broad mix of skills and experience needs to be reflected in the governing bodies that oversee the entire drug portfolio.

A governing body that embraces a value-driven drug-development approach will need a strategic perspective on the portfolio in order to assess the relative risk/benefit profile of any single compound within it and decide which compounds to resource and prioritize.

Like the development team, the board will need people with a mix of scientific and business skills and experience, and in particular an understanding of the health care systems in different geographies. This mix will help ensure the board maintains a strong external focus, watchful of what competitors are up to and what the market requires, and providing the right guidance to development teams. It plays an important coaching role, challenging teams constructively to ensure strategies are robust.

4. Instill a performance culture that encourages innovation and maximizes value

Value-driven drug development has a much broader exploratory remit in Phase 2 than is currently the case. This has repercussions. For example, because Phase 2 seeks to establish the extent to which a compound differs from those that are or will be available, decisions will be taken early on whether to continue or halt development. This is likely to increase the attrition rate of Phase 2 projects but could reduce Phase 3 attrition. In addition, a value-driven approach might shift resources from compounds showing marginal differentiation, even if they are in large indications or segments, to those with greater differentiation but in a narrower segment of the population—for example, from hypertension, to hypertension in the Afro-American population.

This exploratory approach requires a greater degree of transparency, risk-taking, and innovation. To some it might feel liberating, but others might find it unnerving. Companies thus need to foster a culture that supports the new approach, whereby value generation is the key criterion in all important processes.

New performance measures and incentives will help. Currently, development teams are rewarded for meeting milestones on time. In the new paradigm, a team that is upfront about the risks of a project, or willing to make the tough decision to terminate an unpromising one because of limited differentiation, will still be rewarded because it has kept its eyes firmly on the value goal. Similarly, a clinician who fails to show a compound is different from the future standard of care but uses an innovative, cost-saving trial to do so, is still congratulated. The clinician who uses a traditional approach just to avoid risks and shows mild differentiation compared with a placebo, is not.

Cross-functional collaboration is key, but not easy to build. Those accustomed to working in silos tend not to like having their ideas or working practices questioned. A culture that encourages the constructive challenging of ideas and strategies will help break down silos, as will a willingness to dissent and to raise concerns when needed. Those at the top of the organization and in positions of authority—boards and team leaders—will have to show the way. Only when they model the new methods of working will others be likely to adopt them.

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Most companies will need to transform their R&D organizations entirely to incorporate a value-driven approach capable of developing innovative drugs with demonstrated value. This will affect the composition of teams, governance, culture, and capabilities.

Our experience suggests a pragmatic approach is best. Although the architecture of the transformation program needs to be clear, not every detail of the design has to be settled before embarking on change. Better to start quickly by piloting different elements of the program, thereby helping management to understand rapidly what works and what does not and to make any necessary refinements. Staggering the program's components also makes sense to avoid overwhelming the organization.

Certainly, such a transformation will stretch executives in R&D and commercial areas as well as their product teams. But done well, it will also unlock the value of the pipeline and deliver a step-change in the performance of the organization.

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