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Bench to Bedside

Why Successful Drug Development Requires a Team Approach

BioProcess International
SPECIAL REPORT

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Why Successful Drug Development Requires a Team Approach

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The path to bringing new drugs to market is becoming more difficult to navigate than ever before. In addition to rising research and development (R&D) costs and regulatory complexities, drug developers also must consider patient perspectives, market access and reimbursement concerns, manufacturing challenges, and increasingly complex science and technologies, particularly with the emergence of advanced therapies such as cell and gene therapies.

Despite these challenges, early stage drug development is experiencing explosive growth and innovation that include increased identification of novel targets, novel delivery systems, and new therapeutic approaches. But innovation in the later clinical stages of drug's lifecycle have not kept pace. This stage is a significant source of inefficiency in the process. The ongoing pandemic and development of the COVID-19 vaccines in record time has shown us that later stage development can be done more efficiently and faster, drawing attention to the need for revamping certain aspects of the development process. Changes that will drive greater efficiency include virtualizing clinical trials, conducting studies in overlapping rather than sequential ways once safety has been established, and adopting more cross-functional, collaborative, and integrated ways of working.

The process from development to market approval for new drugs takes many years and requires both integration and orchestration of a number of activities based on deep scientific and market expertise. We tend to think of drug development as a sequential, phase-driven process during which a product is taken methodically from discovery through preclinical phases and clinical development, then ultimately to market. In reality, new drug-product development is not linear; rather, it involves integrated collaboration among different functions and stakeholders from the outset to ensure success.

The same goal applies to every functional area involved in delivering new drugs to the patients who need them. However, each group contributes different expertise, and all teams must come together seamlessly to achieve success. Too often, the different activities involved in drug development are conducted and managed in functional siloes rather than through integration. Those can include nonclinical; regulatory; chemistry, manufacturing, and controls (CMC); toxicology; clinical; statistics; pharmacovigilance; and market-access specialists. A lack of integration and coordination among those functional strategies and activities can affect a development program adversely in several areas, from regulatory submissions to process development, outsourcing, and marketing.

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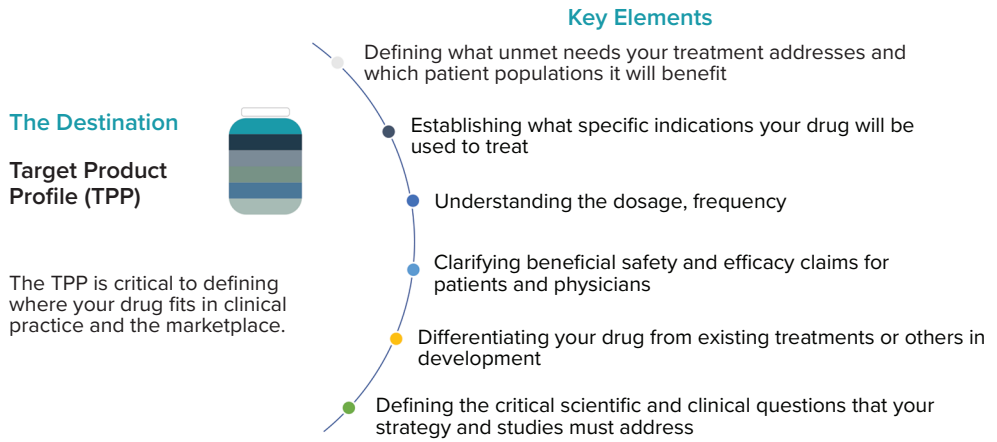
• Submission of an investigational new drug (IND) application and the subsequent start of a clinical

Figure 1: Key elements of a target product profile (TPP) form the basis of an integrated development program.



program could be delayed if no drug supply is available in time to support IND-enabling animal toxicology studies.

• Key clinical trials, and possibly product launch, could be delayed if a company fails to consider packaging and labeling lead times for preparing clinical trial supplies.

• Program timelines — and ultimately, product launch — can be delayed when companies don't account for timelines related to meeting and scheduling requests with and responses from the health authorities. Similar delays can occur if process developers do not factor in adequate time to prepare briefing documents.

• Significant cost overruns and delays might be incurred if alternative plans for incorporating regulatory feedback or emerging clinical trial data are not considered in advance.

• Not integrating market-access considerations with patient engagement early in clinical development could bring clinical outcomes that do not meet expectations of regulators and payers. Consequently, developers might be obliged to conduct further studies.

• If startups and small biotechnology companies fail to engage key stakeholders — e.g., contract development and manufacturing organizations (CDMOs) and contract research organizations (CROs) at the right time — such sponsors can incur high costs associated with delayed time to market as well as from duplication of effort and wasted time.

Those and many other issues can be prevented or mitigated if a bench-to-bedside, integrated product development approach is established early in a program lifecycle. Considering the end goal and how the numerous puzzle pieces must fit together helps ensure that new therapies can be brought to market without costly delays, budget overruns, or failed and/or repeated studies. A globally integrated product development plan is an essential tool for improving efficiency, shortening timelines, reducing costs, and improving the probability of regulatory approval and success in the marketplace.

Desired claims and critical medical and scientific questions inform the number, type, design, and timing of the clinical and nonclinical studies needed to support product APPROVAL and market SUCCESS.

An integrated product development strategy begins with a clearly defined destination. Without careful, coordinated planning and a well-defined objective, the drug development process is liable to stray off course. Of course, science and data influence the direction of a program, but the end goal must be kept in mind along with the necessary strategies to achieve it.

Program Objective and Destination

The destination in integrated drug development is a target product profile (TPP). Developing a TPP is a team activity that requires input not only from different drug development functions, but also from experts in regulatory and market intelligence who understand the competitive landscape with its

In practice, when creating an integrated development strategy, teams need to look for opportunities to conduct activities **IN PARALLEL** to improve efficiency and reduce timelines and costs.

changing expectations of patients, physicians, and payers.

Although a TPP will evolve as development progresses, it can and should begin early in development with just a few basic components. A useful approach in developing a TPP is to define both minimally acceptable and best-case scenarios. The minimal version defines the attributes of a drug that absolutely must be achieved to ensure that drug's viability on the market and justifies required investments; the best-case version is a success story (the "blockbuster" of previous years) that, if achieved, will generate significant return on investment.

Figure 1 shows key elements of a TPP that form the basis of an integrated development program. For example, defining a patient population, indication(s), and safety and efficacy claims are critical considerations for determining regulatory strategy. Understanding the dose, frequency, and route of administration required to make a drug competitive and differentiate it from the competition drive the CMC strategies that will define your clinical and regulatory program. Desired claims and critical medical and scientific questions inform the number, type, design, and timing of the clinical and nonclinical studies needed to support product approval and market success. The core elements of your TPP help define what you need to know, when you need to know it, and what success will look like.

Those examples also illustrate the interconnectedness of different company functional groups and the need for an integrated development strategy. The hard work of integrated product development begins with crafting that strategy and associated plans that will be needed to deliver a successful outcome. Developing a globally integrated product development strategy requires a team effort led by an experienced integrated product development leader who is familiar with drug development challenges and pitfalls, who can anticipate them, and who will accompany the project team members along their journey, challenging their assumptions and strategies and optimizing development plans to deliver successful outcomes.

Members of those different groups should come together as a cross-functional team to discuss their strategies and plan what is needed to achieve the TPP. They need to lay out key risks carefully and determine how those will affect timing. For example, risks identified at the pilot-scale stage could delay timing for delivery of drug product needed for initial clinical trials. In turn, such a delay can affect regulatory, clinical, and other strategies, plans, and timing. This illustrates another key consideration in developing an integrated strategy: Once critical risks have been identified, the functional teams need to develop mitigation steps and alternative plans focused on reducing delays, or the overall program could face significant cost overruns.

Take care not to assume that development activities are completed sequentially. In practice, when creating an integrated development strategy, teams need to look for opportunities in which conducting activities in parallel can improve efficiency and reduce timelines and costs.

An integrated product development roadmap describes strategies and key deliverables for regulatory, clinical, CMC, nonclinical, and commercial strategies. Other functions also are critical in helping to inform those strategies: e.g., statistics, data analysis, operations, quality management, and pharmacovigilance specialists. An integrated strategy also should include major development milestones, decision points, and potential timelines for key activities and for the overall program. Note that this is not a project-management plan, which is a much more detailed and comprehensive exercise.

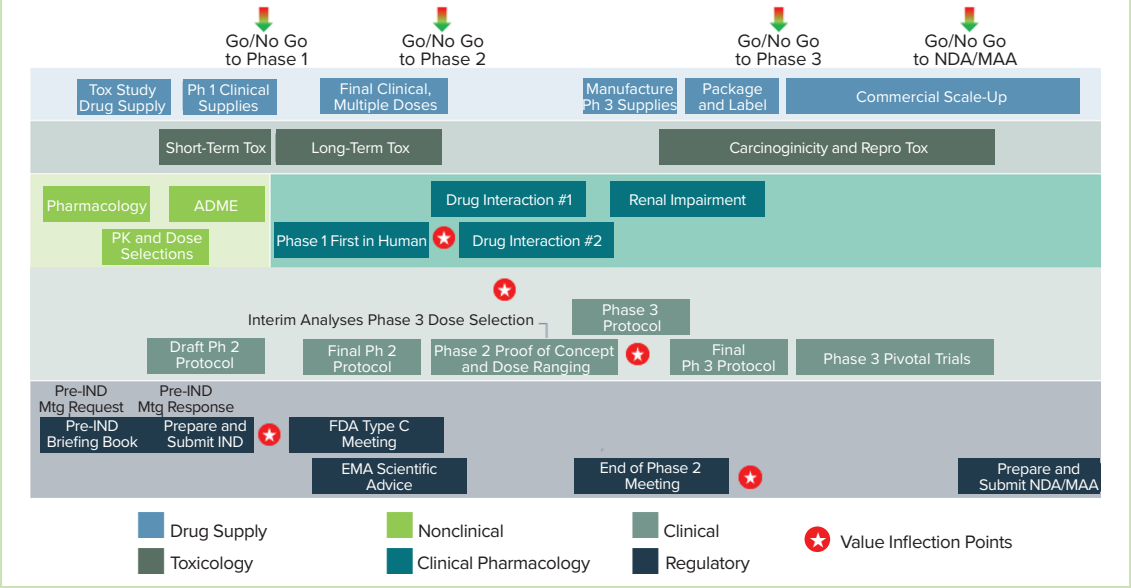
Figure 2 depicts a much-simplified illustration of a potential global development roadmap, highlighting some of the interdependencies that often connect key functional teams.

Regulatory and Clinical Strategies

For better understanding of integrated product development, it is important to consider the different functions and stakeholders involved and the role that each of them plays in reaching the program destination.

From the outset, understanding the **regulatory environment** and the ways in which requirements, precedents, and perspectives differ across countries and regions is key to navigating product development successfully. Regulatory considerations significantly influence the design and execution of a

Figure 2: A simplified illustration of a potential global development roadmap shows some of the interdependencies among key functions.



global drug development strategy. Some examples of important regulatory considerations include

- the recommended pathway to approval (which may differ from one region to another)
- special regulatory mechanisms for expediting drug development (e.g., breakthrough-therapy designation granted by the FDA, conditional marketing authorization granted by the European Medicines Agency, orphan-drug designation, and so on)
- regulatory intelligence, including competitive-landscape analysis
- major regulatory submissions and interactions for development, scientific, or protocol advice
- design of key/pivotal studies and types of endpoints.

Another central part of an integrated product development plan is the **clinical program,** which defines all clinical studies required for approval and market success, including from first-in-human, through proof-of-concept to pivotal trials and eventually lifecycle management.

We often think of clinical programs as driven by a phase of development (phase 1, 2 or 3). A more efficient and time-saving approach is to construct your clinical program around critical questions defined in the TPP. For example, to enter a market in which competitive products are all intravenous, you might want to conduct a trial early in development to understand the bioavailability and efficacy of your drug candidate when administered subcutaneously, thus creating a significant competitive advantage. Or you might consider whether your drug candidate can be administered safely to patients with hepatic or renal impairment. Depending on the TPP, if you conduct appropriate studies early in development, you might be able to prevent label restrictions for those populations.

Although many first-in-human studies are conducted in healthy volunteers, you might be able to include a cohort of patients with the target disease near the end of a study once safety has been established. Such an approach could enable early assessment of target engagement or pharmacodynamic effects in a target population, potentially providing an early indication of effectiveness and offering insight into the design of subsequent trials.

All pharmaceutical/drug development programs need a strategy to ensure that ADEQUATE product SUPPLIES will be available when needed for all phases of development and, ultimately, commercialization.

CMC Strategies

All pharmaceutical/drug development programs need a strategy to ensure that adequate product supplies will be available when needed for all phases

It is critically important to seek **REGULATORY** agency input on your nonclinical program to ensure that your studies support not only safety, but also dose selection and other considerations for the initial clinical trials.

of development and, ultimately, commercialization. In addition, the drug substance needs to be available in a formulation or presentation that is suitable for the route of administration detailed in the TPP. That drug product must meet nonclinical and clinical study needs in accordance with regulatory requirements, such as compliance with good manufacturing practice (GMP) status. In addition, important considerations for the CMC strategy include the following:

- optimizing drug production, downstream process development, drug-product manufacturing, and scale-up
- controlling the cost of goods and supply-chain management
- understanding the demand and anticipated surplus for clinical studies and market launch
- planning for quality control, packaging, labeling, and shipping
- identifying risks such as issues with stability, potential impurities, or metabolites.

A detailed CMC plan must be integrated into the overall program plan to ensure that key analyses and reports are made available to support regulatory submissions and agency meetings and that there will be no delays to planned clinical or nonclinical studies. Even worse would be a need to transfer manufacturing to another site.

Nonclinical Studies

Depending on the kind of therapy being developed, several types of nonclinical studies might be required during a development program. Those could include pharmacology and pharmacokinetics, toxicology, genetic toxicology, safety pharmacology, metabolism, and bioanalytical studies. Nonclinical studies must comply with regulatory guidelines and provide data to assure health authorities that the therapy has shown preliminary evidence of safety and efficacy and is suitable for use in clinical trials at the planned dose levels over the expected treatment duration.

A full, standard battery of tests not always is needed before beginning clinical studies. In fact, some tests might not be needed at all, depending on the specific therapy being developed and how it will be used in patients. For example, if a drug is to be used only for short-term administration, then longer duration toxicology studies might not be required. Key aspects of a nonclinical strategy include dose selection and choice of animal species, critical questions to be addressed, and the rationale and relevance of each study. It is critically important to seek regulatory agency input for your nonclinical program to ensure that your studies support not only safety, but also dose selection and other considerations for the initial clinical trials.

Commercial and Market Access Aspects

In the not too distant past, most effort in drug development was focused on attaining regulatory approval. Commercial considerations entered very late into most programs. Although achieving regulatory approval after following a well-considered drug development plan is a major accomplishment, it is insufficient in itself to ensure maximum benefit to patients or to achieve commercial success and return on investment.

Now more than ever, patient and market considerations must come into play early in a development program, beginning with the TPP. Patient perspectives on route and frequency of administration, duration of treatment, side-effect profile, quality of life, and cost — among other things — must be considered early on. Understanding the competitive landscape and establishing differentiation from the competition are additional critically important aspects of a TPP. To ensure market success, a commercial strategy must consider perspectives from a number of stakeholders in addition to patients: e.g., physicians, professional medical organizations, insurers, and advocacy groups. Formulating a commercial strategy early in development can help a drug sponsor to identify important factors that can influence success in the marketplace. Those can include important endpoints to identify in clinical trial designs, for example, or specific studies that will be needed to support reimbursement once a product is approved.

Working Collaboratively for Success

The need for an integrated team approach is somewhat intuitive, yet it is surprising how few companies adopt truly integrated strategies and planning in their development programs. Rather,

they continue to operate in a siloed fashion or approach development sequentially by moving from one phase or milestone to the next without considering the impact on other functional activities or on subsequent development steps. One key obstacle to integrated development is the use of operating models and decision-making that do not support integration, agility, and rapid decision-making. Too often, the various activities, deliverables, and associated decision-making involved in drug development — nonclinical, regulatory, CMC, toxicology, clinical, statistics, pharmacovigilance, market access, among others — are conducted and managed in functional siloes rather than integrated. Functional leaders often insist on retaining decision rights regarding program resourcing and timelines for their specific deliverables, thus limiting the ability to make cross-functional tradeoffs that would optimize the overall development program. A lack of integration and coordination of functional strategies and activities can adversely affect a development program. From cost overruns or delays to an inability to meet program timelines, the lack of team integration can derail plans.

Creating an integrated product development plan requires a team approach in which many different functions and experts contribute to the overall program design and execution. Establishing your destination — your TPP — will guide the development program and ensure that those teams, your company's senior leadership, and other key stakeholders remain aligned and focused on the common goal.

Inevitably, a TPP and associated plan will evolve over time with additional detail and refinement after achievement of development milestones. A well-designed, integrated product development roadmap brings together the key activities that support a well-defined goal and maximize the probability of delivering new therapies to patients. A bench-to-bedside holistic approach helps drug developers avoid pitfalls that can delay or perhaps even kill their programs. Such an approach helps to shorten timelines and lower development costs, improve the probability of commercial success, and, crucially, bring life-saving or life-changing products to patients in need.

When outsourcing various functional services, sponsor companies often use multiple vendors or consultants. Although potentially cost-saving, this approach leads to less collaboration and integration and ultimately to unforeseen delays, cost overruns, and rework. At PharmaLex we offer "bench to bedside" integrated product development services spanning all of the necessary functions. Our Global Center for Integrated Development offers the expertise and knowledge needed to guide development and bring new assets to the market. If you would like to discuss the ideas in this article or learn more about our services at PharmaLex, please reach out to me at the address below.

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