WHITE PAPER

Strategic roadmap for drug development: Enhancing efficiency and reducing costs while increasing the probability of success

A KEY QUESTION

How can an integrated strategic approach to drug development improve efficiency, reduce costs, and increase the likelihood of successful regulatory approval and probability of success?

KEYWORDS Drug Development Plan (DDP), Target Product Profile (TPP), Regulatory Strategy, Biotech

Less than about 10% of novel compounds that enter initial Phase I clinical trials will obtain regulatory approval for marketing. Therapeutic efficacy and safety of a new compound are necessary, but not sufficient to assure cost-effective development, or successful launch and commercialization.

As an expensive and complex process, drug development requires the coordinated efforts of diverse disciplines, including nonclinical, clinical, regulatory, and commercial experts. On the path to market, pharmaceutical and biotechnology companies face many obstacles and potential pitfalls, which can cause costly delays or stop progress entirely. This white paper provides an overview of creating an integrated drug development plan, an important tool for identifying development challenges and devising strategies that increase the likelihood of delivering a new, approved medicine to patients.

What is the role of a comprehensive development strategy?

When starting a new drug program, experienced pharmaceutical companies devote considerable effort creating a comprehensive development strategy. This plan provides a detailed roadmap for advancing a new compound from the lab through each stage of development, ultimately arriving at the envisioned marketed drug product. A well-thought-out strategic development plan is an essential tool for improving efficiency, reducing costs, shortening timelines, and increasing the probability of success for a new drug program.

A multi-disciplinary project team of experienced experts collaborate in preparing this plan, which outlines the key nonclinical studies and Phase I-III clinical trials, chemistry, manufacturing and controls (CMC) and formulation activities, regulatory submissions and health authority interactions, as well as commercial launch activities and life-cycle management. By identifying potential development issues and challenges, the strategic plan can include alternative development options or scenarios that help companies avoid or mitigate risks.

The strategic plan also outlines major development milestones and success criteria, and can facilitate cost and timeline estimates that provide a basis for sound investment decisions and project portfolio prioritization and management.

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The major parts of a
comprehensive drug development strategy
include the target product profile (**TPP**) and the plans for

Regulatory · **Nonclinical** · **Clinical** · **Commercial** · **CMC**

Integrating all of these elements together in a seamless strategy document is a critical first step on the road toward realizing a program's ultimate goals.

What is a target product profile (TPP) and why is it needed?

"If you don't know where you are going, how will you get there?"

An important first step in creating a strategic roadmap for a drug development program involves clearly defining a destination that encompasses the key characteristics of the marketed drug product. Internal and external experts collaborate to outline the desired final product attributes. These include the target indication or disease(s) to be treated, patient population(s), therapeutic efficacy and clinical safety, formulations, dosing regimens and administration, drug-drug interactions and contraindications or precautions, among others.

A TPP is a compilation of these characteristics and provides a basis for guiding the design of all program activities, such as nonclinical and clinical studies, to ensure they will provide the information needed to assess whether the drug has the desired attributes. Clinical trials and other nonclinical studies will then be focused to answer critical questions at the earliest possible stages of clinical development. For example, does the drug have pharmacokinetics that permit once-a-day dosing, or is therapeutic efficacy better than currently available therapies? Such information provides essential positioning for a competitive drug product.

The TPP also helps set criteria for critical investment decisions. For example, based on initial Phase I and II trial efficacy and safety results, should the drug candidate be advanced into lengthy, expensive Phase III development?

Creating a TPP brings many questions into sharp focus and drives efficient development program planning, but the TPP is not a static document. To ensure ongoing development remains on track, the TPP evolves with new information from clinical trials, nonclinical studies, and the external regulatory and commercial environment. In this way, the TPP eventually provides the basis for preparing the final approved product label.

For a novel drug candidate that has not yet entered clinical testing, research scientists may provide only their best estimates of the final product's attributes based on nonclinical data. Nonetheless, clinicians can use the initial TPP to begin assessing how the envisioned drug product will meet a medical need while commercial experts can begin to plan where the drug should be marketed, how the drug would fill a market niche, and also attain reimbursement. Regulatory experts start assessing how health authorities will evaluate the new drug product and what types of data should be sought in both nonclinical studies and clinical trials to gain approval. Such initial considerations guide planning each of the strategic components of the integrated development plan that are described below.

What is a regulatory strategy, and why is it needed?

Drug regulations can be complicated, and often vary among countries/regions. Regulatory agency perspectives on development topics can evolve, significantly affecting how a new program should be designed and executed. A detailed understanding of regulatory requirements and health authority viewpoints is central to planning a drug development program.

A regulatory strategy can include:

- **The recommended pathway** for regulatory approval, based on relevant regulatory guidelines and precedents from the agencies (e.g., FDA, EMA, PMDA, SFDA) in the market(s) of interest. This can also include a description of alternative approval pathway options, explaining pros and cons, and providing the rationale for the recommended option
- **Regulatory intelligence**, such as an evaluation of the regulatory paths taken for similar drugs (if applicable), whether these drugs were approved (or not), or still in development. A diligent analysis identifies any special regulatory agency requirements that may apply to a new drug
- **A timeline for major regulatory submissions** (e.g., IND, NDA/BLA for U.S. FDA and similar filings in other countries), and additional agency interactions (e.g., pre-IND, and End-of-Phase II meetings) that will provide feedback to address questions and ensure the program ultimately will meet agency expectations
- **Plans for agency interactions**, which include the goals and objectives of each major meeting, an outline of the key questions that need answering, as well as how those questions should be asked
- **Key studies and types of trial endpoints and data** that regulators will need to see at each stage of drug development; identification of potential regulatory agency concerns and challenges. This helps ensure that nonclinical studies, clinical trials, and CMC activities provide the necessary data
- **Special options** for accelerated review and approval, or market exclusivity that may be applicable to the drug (e.g., fast-track, breakthrough, and orphan disease indication status)

What is a clinical development strategic plan?

A carefully planned set of clinical trials, progressing from first-in-human Phase I to Phase II "proof of concept" and pivotal Phase III trials for registration is a central part of a comprehensive development plan. Clinical trials are often the most expensive and rate-limiting part of a program, so considerable effort goes into designing trials that are both necessary and sufficient for regulatory approval and market success. These trials will also provide the data for making investment and/or partnering decisions at intermediate points during development.

To begin designing a clinical trial program, physician-scientists first review the preclinical profile of the new drug candidate (e.g., its pharmacology, mechanism of action, and toxicology) and summarize their assessment of how such properties may impact clinical trial design, as well as proposed therapeutic use in patients. The medical and scientific rationale for the drug product is assessed to ensure that the marketed product is likely to gain acceptance by healthcare providers, patients, and professional medical organizations.

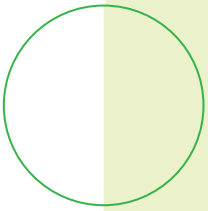
The clinical plan can include:

- **Summary outlines of each key trial**, from initial Phase I through Phase III, including the study objectives and clinical hypotheses, trial design, key endpoints and measures (e.g., for safety, efficacy, pharmacodynamics, pharmacokinetics, surrogate markers, biomarkers, and patient-reported outcomes, etc.), as well as subject populations, key inclusion/exclusion criteria, and approximate subject numbers, and treatment durations. More detailed trial descriptions (e.g., clinical trial protocol synopsis and operational feasibility assessments) can also be appended to a development plan, if needed
- **A "proof-of-concept" definition.** When an early "Go/No-Go" milestone decision is required to decide if the drug can meet the TPP (e.g., as might be needed for continued investment or to inform partnering/licensing decisions), a Phase I or II study can often be designed so that results enable a well-founded decision. The clinical development plan can also provide specific "Go/No-Go" decision criteria. Articulating and justifying such important criteria can involve detailed consultation with statisticians and other project team members, as well as senior company management
- **Post-approval plans** for additional clinical trials and related clinical activities, that can include the following:
    - Phase IV trials to explore additional therapeutic indications, or to compare a new drug's effects versus competing drugs/therapies to demonstrate health economic value and support reimbursement by insurers, or to evaluate new drug formulations that may provide additional patient convenience or benefits, or to gain approval for use in special populations (e.g., pediatrics)
    - Specific commitments made to regulatory agencies as a condition for initial approval (e.g., cardiovascular safety trials for diabetes drugs)
    - Risk Evaluation and Management Strategies (REMS) plans that are sometimes needed following approval to monitor specific safety concerns and/or meet regulatory pharmacovigilance requirements
- **A high-level timeline** that helps in coordinating and scheduling other program activities and triggering financial and resource investments (e.g., for drug manufacturing and scale-up, formulation development, toxicology and drug metabolism studies, or validation of biomarkers and/or companion diagnostics, or seeking regulatory agency advice)
- **An evaluation of any major clinical development issues or risks**, including ways to address potential contingencies or mitigate challenges, with options for modified or alternative development scenarios. Every drug program is unique, but lessons learned from prior programs (internal and external) can often be applied to recognize and avoid pitfalls in new programs

What is a CMC strategy, why is it important, and how is it prepared?

Every new drug development program needs a plan for maintaining adequate drug supplies for each phase of the program, with a formulation suitable for the intended route of administration that meets all nonclinical and clinical trial needs, as well as all regulatory requirements. A CMC plan functions as a vital component of a fully integrated development plan by outlining the major features of a drug supply and formulation strategy, as well as any placebo or comparator drug supply needs. A CMC plan includes an assessment of the estimated cost of goods (COGs) for the drug substance and final market product, a key factor in new drug development.

Preparing a CMC strategy often begins with a thorough technical, scientific, and regulatory review of all available data on the drug substance or API (active pharmaceutical ingredient). The review also examines any existing pilot drug formulations to assess whether the available CMC data can be used to support the proposed nonclinical studies and the clinical trials and can also meet relevant Good Manufacturing Practices (GMP) regulatory requirements. That review can outline any additional CMC work needed during development, for example, to ensure drug supply availability, stability, and purity, with analytical methods for quality control that meet required specifications.



COMPONENTS OF A CMC PLAN

- Assessment of any existing drug synthesis, manufacturing, or scale-up procedures and costs
- Plans for quality control, packaging, or shipping
- Recommendations for future drug production processes, based on the proposed clinical trials (considering their timing, size, and geographic location)
- Expected demand once the drug is on the market
- Drug-specific liabilities (e.g., chemical instability or high synthesis costs) that could jeopardize approval or market success
- Recommendations to preclude or mitigate potential risks

What is the nonclinical strategy and plan?

Advancing a drug into initial Phase I trials requires completing numerous nonclinical studies. These studies must comply with detailed regulatory guidelines, such as GLP or ICH, and convince regulatory agencies and oversight committees or review boards that a drug is suitable for administration to people at the planned dose levels. Nonclinical studies typically include toxicology, genetic toxicology, pharmacology, safety pharmacology and drug metabolism, pharmacokinetic, and bioanalytical studies, among others.

Later Phase II and III clinical development and regulatory approval for marketing requires additional nonclinical studies, for example, longer-duration toxicology and reproductive toxicology, carcinogenicity, and bio-distribution studies. Special studies may also be needed to address concerns unique to a specific drug, or its molecular target and mechanism of action.

IMPORTANT ASPECTS OF A NONCLINICAL STRATEGY

- Choice of animal species and selection of doses in toxicology studies
- Recommendations and rationales for study designs, and relevance of nonclinical studies
- The role and timing for regulatory agency input

Preparing the nonclinical strategy begins with a thorough technical, scientific, and regulatory review of all available nonclinical reports and findings, including *in vitro* and *in vivo* studies. Based on an assessment of whether the available nonclinical data are scientifically sound and adequate to support the proposed clinical trials and meets all relevant regulatory guidelines, the nonclinical plan will recommend and describe any additional nonclinical studies needed to support the proposed clinical trial program and final regulatory approval for marketing.

During this process, the nonclinical expert interacts closely with colleagues in other disciplines. For example, if a nonclinical *in vitro* drug metabolism study suggests a drug-drug interaction that might have significant implications for patient safety, or for commercial viability, a recommendation might be prepared for conducting a specific drug-drug interaction clinical trial. If the trial is completed during early development, the results can be used in early Go/No-Go decisions, help aid clinical dose and formulation selections, or inform decisions involving combination drug treatments in later Phase II or III trials.

What is a commercial strategy plan, and why is it important?

Completing an entire drug development program and obtaining regulatory approval for marketing a new drug is a major accomplishment, but this does not guarantee commercial success or maximum return on investment nor ensure optimal opportunity for patients to benefit from the new product. Successfully penetrating the healthcare market after launch to assure rapid adoption by prescribers and wide use by patients requires a well-planned commercial strategy that favorably positions the product with key opinion leaders and stakeholders, including physicians, professional medical organizations, and insurers who make reimbursement decisions.

Planning a commercial strategy begins with a thorough review and analysis of the competitive landscape for the product against currently available treatments, considering their effectiveness, side effects, costs, and patients' and physicians' satisfaction with existing therapeutics, along with upcoming treatments that are in the pipeline.

This exercise informs how the drug can be differentiated from competitors, what types of data should be obtained to best demonstrate value and contributes to determining the target drug price, as well as the economic value (e.g., NPV) of the drug asset. Whether conducted during Phases I-III, or following approval in Phase IV studies, a competitive landscape analysis can also influence the design of the program's clinical trials. For example, before granting reimbursement, insurers can require strong evidence that an innovative new drug provides patient or health economic benefits that offset its typically higher cost versus low cost generic drugs. Insurers or payers may also ask, "If the new drug is prescribed together with another standard of care treatment, will it provide additional therapeutic benefit?" Being prepared to answer such questions can make a major difference in market access for the new drug.

A commercial strategy can identify the most important health economic endpoints to include in clinical trials or suggest how to obtain relevant data via approaches other than traditional interventional clinical trials, such as real-world evidence based on analyses of patient healthcare databases or pharmaco-epidemiological studies, which can be used to convincingly demonstrate the drug's value and justify pricing.

Beyond the initial approval and commercial launch, life-cycle management encompasses ways to extend and maximize the therapeutic and commercial value of a newly marketed drug. It can include designing additional development programs for supplemental regulatory approvals, (i.e., to market the drug for other diseases or conditions). A complete commercial strategy that includes such life-cycle strategies helps companies understand long-term commercial potential and can influence even very early program investment decisions or partnering considerations.

Formulating a commercial strategy, even at very early stages of planning a drug development program, can identify critical success factors that might otherwise be overlooked. It can also recommend the best methods for obtaining relevant data and effectively communicating results to stakeholders to maximize market access and the value of a new drug product.

Why is a clear roadmap to market needed?

Creating a comprehensive development strategy is a smart investment for both established large pharmaceutical companies and emerging biotechnology companies. The effort of considering and integrating the many facets of a program in this strategy can help avoid pitfalls that could delay or even kill a program, and can reduce timelines and development costs and improve the odds of successful regulatory approvals globally.

A well-thought-out development plan that integrates all key activities and demonstrates a clear roadmap to market not only engenders confidence in a project by senior management—and potential partners—but also serves as a tool that maximizes the likelihood of successfully bringing the benefits of your new medicine to patients.

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