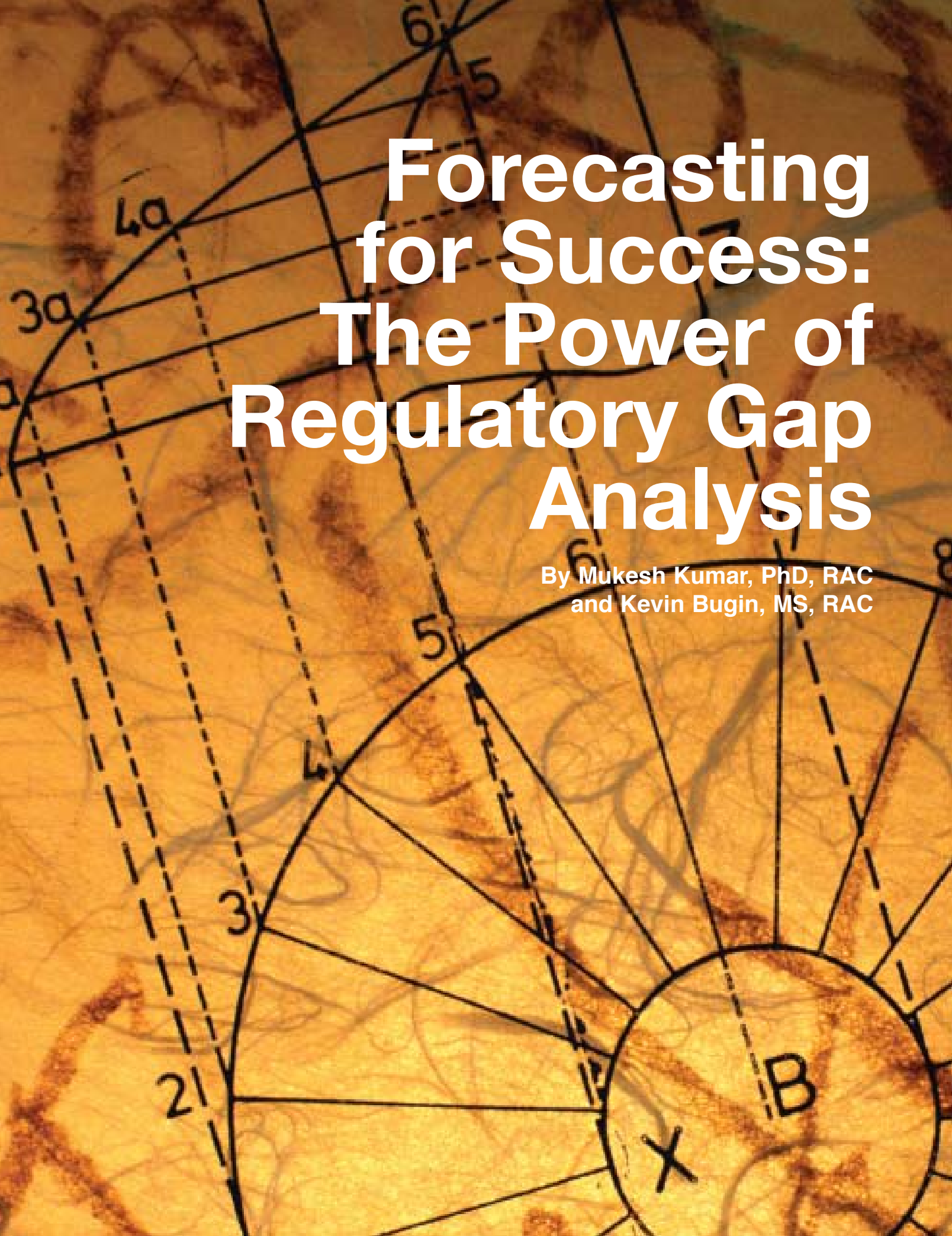

Forecasting for Success: The Power of Regulatory Gap Analysis

By Mukesh Kumar, PhD, RAC
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With the ever-changing regulatory environment and rapid developments in science, it is hard to keep track of the development strategy for a biomedical product. The best available data and development strategy today might not be good a couple of years from now. One must track not only one's own work but also overall developments in science and worldwide regulatory reviews of similar products, as well as market trends and changes in the political and legal environment. Fewer than 1% of all biomedical products conceived move beyond preclinical testing, and fewer than 10% of products that reach clinical testing make it onto the market. Experts estimate the cost and time to develop a successful drug at about $1.3 billion (US) and 10 years (see **Figures 1** and **2**). The bulk of this time and money is spent in preclinical and clinical development. Newer drug development models aim to reduce the time and cost of successful biomedical product development.[1] However, there is no substitute for a timely assessment of the situation and effective strategies to minimize regulatory failure and shorten time to market. The strategy for regulatory approval could be just as unique as the product itself.

Gap Analysis

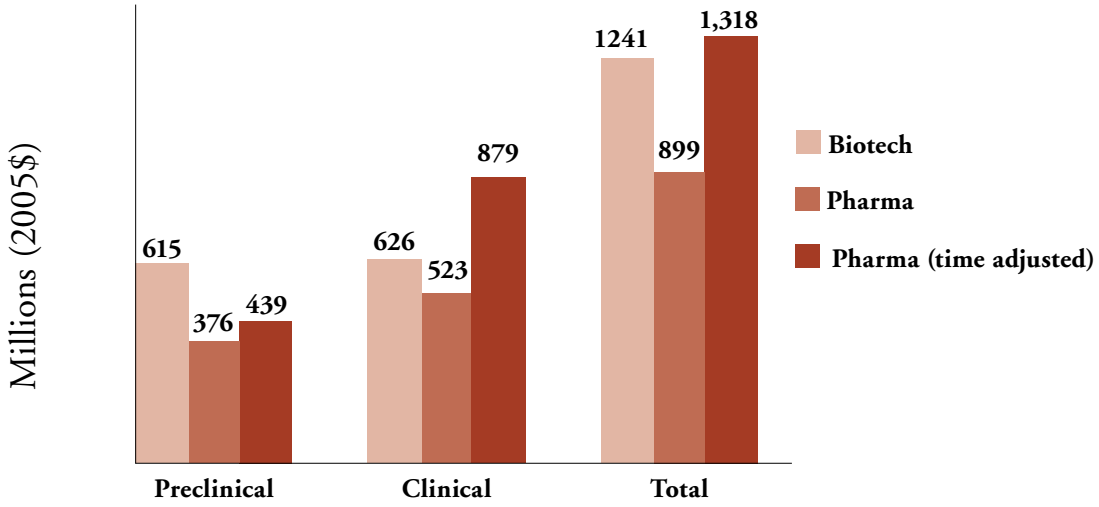
Often, potential candidates go through extensive formulation development and preclinical testing before reaching the clinical testing stage. Almost all candidates, except very specific biological products, have multiple applications in diverse indications. Even biological products could have multiple related indications and target populations. Many factors must be considered before picking a particular development strategy. **Table 1** is a list of strategy development processes.

The process of reviewing all available information for a candidate product to assess current development status, identify potential gaps in the information required for subsequent steps, and develop a strategy to fill those holes is called a gap analysis. A gap analysis is based upon an assessment of the product's current development status in light of the prevailing regulatory requirements, and aims to improve the chances of faster regulatory approval presenting data more effectively and minimizing unnecessary processes. This article focuses on the gap analysis process and the steps involved in the early planning and implementation of the results.

The gap analysis process should begin early in formulation or preclinical development, with the ultimate goal of understanding the potential product's unique nature. To do this, one needs to review all background information for both the candidate product and similar products. **Table 2** lists the information typically reviewed and the minimum points of consideration needed to propose a regulatory strategy. Items in Table 2 that have not already been established for the candidate product should be carefully planned and proposed.

While background information should be easily obtained from the developers in the early stages, details will often be redundant and burdensome. Careful attention should be paid to identifying minimum information needed for regulatory milestones and discussions with regulatory agencies. For example, a product being pursued for first-in-man studies should be evaluated to determine the minimum required cell culture and animal studies; adequate chemistry, manufacturing and control (CMC) information; background scientific information; and the rationale for picking the target indication and populations. A common mistake is trying to do all the studies proposed in the guidance documents without adequately addressing the value each study brings regarding the scientific rationale to support the proposed product. Appropriate justification of not only each study planned but also for not including some studies in the development plan exhibits better understanding of the science behind the product and builds credibility with regulatory reviewers. A key to establishing trust in a plan is demonstrating that one has conducted an extensive review of the regulations,

Figure 1. Cost of New Biomedical Products[2]



R&D Costs (basic research and preclinical development) prior to initiation of clinical testing based on a 4 year shift and prior growth rates for the preclinical and clinical periods

guidance documents and scientific information, and addressed all relevant issues.

Predicate or Precedence Search

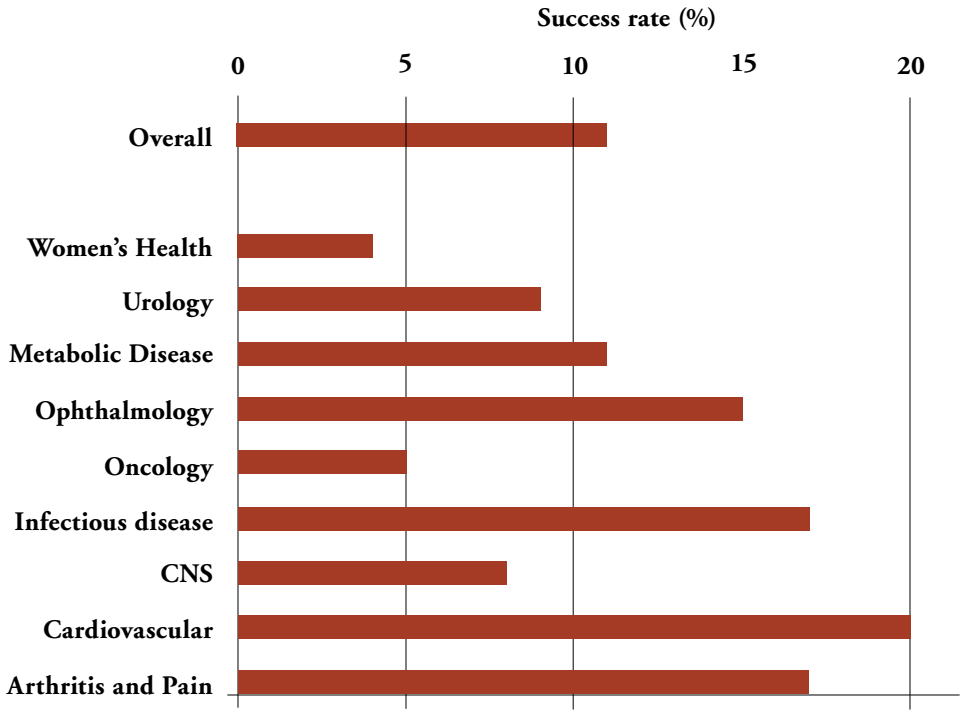
Another important component of this process is the review of information on similar products to find an appropriate model. This type of research is often referred to as a predicate or precedent search. If one knows a similar product has been approved by a regulatory body, information about that product's regulatory review is a good place to begin the search. An earlier approved product would help identify the precedents in the regulatory pathways. However, care should be taken not to rely upon information for products approved more than five years ago, since the regulatory reasoning used for that product's approval might no longer be valid in light of subsequent scientific and postapproval safety and efficacy findings. If there are no similar products approved within five years, an extensive background search of the scientific literature needs to be conducted to support the proposed mode of action and build a sound scientific rationale for the proposed product's safety and efficacy. The US Food and Drug Administration (FDA) is a "science-based" organization, similar to other regulatory bodies around the world, and values good scientific reasoning when making a decision whether to permit a given product's clinical testing and marketing. It is important to dedicate extensive time and consideration to precedent research because it not only forms the basis for proposing a regulatory strategy, but also becomes the major point of discussion with the regulatory agencies and, ultimately, a primary factor for product approval.

There are many locations to investigate during a search for precedents, such as:[5]

- health authority websites
- presentations from health authorities
- previous approvals
- MRI-Product Index (EU Heads of Medicines Agencies)
- labeling
- minutes from interactions with health authorities
- advisory committee briefing packages and transcripts
- postmarketing commitments database
- patent and exclusivity information
- summaries of medical and clinical pharmacology
- pediatric written requests
- Inactive Ingredients Database (US)
- clinical trial disclosure websites (WHO, IFPMA, EUDRACT, PhRMA, ClinicalTrials.gov, etc.)
- competitor information
- compliance issues

The above searches may yield background information, timelines and progression through various stages of development, expert opinions, and

Figure 2. Attrition Rate for New Molecular Entities[3]



detailed reviews of CMC, preclinical and clinical information, postmarketing issues, market size, etc. From this information, one can extract useful details that can be used to define and design endpoints, pivotal studies, demographics, adverse reaction potential, strategy, applicable guidance and regulations, applicable chemistry and manufacturing standards, etc.

Once intelligence regarding the potential product and a development model has been gathered, one needs to focus on the details of the current regulations and guidance. The best place to start is with the health authority that would be responsible for reviewing the potential product, working backward through the approval process with the ultimate goal of highlighting specific regulations. These regulations and the precedent information gathered earlier (with their context) are used to identify the gaps in what is currently available and what is needed for the product to reach the market.

Building a Custom Strategy

Using the above information, one should plan the preclinical, clinical, manufacturing and marketing commitments to balance them against the regulatory requirements and budgetary constraints. The final goal is not to identify all that is needed per the guidance, but to identify the minimum threshold for regulatory review. With today's resource constraints and tight timelines, it is important not only to do all the required studies but also to avoid unnecessary studies, both nonclinical and clinical.

The most important element of the strategy is discussion with regulatory agencies. Both FDA and the European Medicines Agency (EMEA) offer excellent resources for discussion with the reviewer via in-person meetings and other communications. Regardless of how accurate and in-depth the gap analysis may be, it makes good strategic and business sense to discuss one's findings and plans with the very same regulators who are going to review the subsequent applications. FDA meetings are an outstanding resource; they give the opportunity not only to discuss plans one on one with the regulators, but also to understand the agency's concerns and discuss the potential ways to address them before conducting extensive studies.

While they may not seem relevant, business considerations should also be incorporated into this phase of planning. These considerations include the developer's ability to execute the strategic plan and whether new team members, operations or organizational units need to be

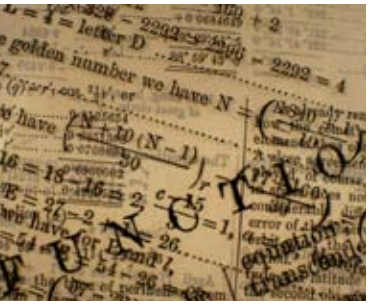


Table 1. Regulatory Business Strategy Development[4]

Process	Description
Selection of the indication and need for special status	The most suitable indication is selected based upon corporate mission and development status. Available incentives are identified, e.g., orphan or pediatric indication, tropical disease treatment, etc.
Preclinical design	Description of in vitro and animal studies required immediately versus deferred until later in the development cycle
CMC design and manufacturing plans	The manufacturing process and the analytical testing needed per cGMPs; selection of the manufacturing facility
Clinical plan	The description of clinical studies required per the current regulations for the indication selected; identification of need for global sites
Identifying the key regulatory agency	Although plans may call for filing approval applications concurrently in multiple countries, it is best to start with one regulatory agency, e.g., FDA, where approval will be sought first to establish the product's regulatory history to be used in subsequent filings in other countries
Marketing plan	Although it might seem premature, it is best to consider product marketing issues as early as possible in the lifecycle for periodic product viability assessment
Postmarketing plan	Understanding postmarketing issues with similar approved products is critical for strategic planning
Tactical regulatory submissions	For multinational studies, regulatory submissions should be filed in a manner that places them in the most favorable condition; for example, filing an IND with FDA first helps obtain expedited approval of the same IND in India

developed or acquired. Additionally, the strategy needs to address specific objectives and time-tables for accomplishing them.

Information from a thorough gap analysis can and should be used as the basis for writing applications to health authorities and designing protocols for clinical development. Over time, as the product proceeds through the various stages

Table 2. Background Information for Biomedical Product Candidates

Review of background information
Product name and chemical nature
Indication (disease intended to treat)
Animal or in vitro experiments carried out to date
Manufacturing details (GMP or non-GMP)
Prior human experience (prior marketing details, adverse experiences, etc)
Product's Strengths, Weaknesses, Opportunities, and Threats (SWOT analysis)

of development, the gap analysis forms the base upon which the entire project is executed.

Conclusion

A gap analysis is a powerful tool that can be used to forecast a particular product's success. It involves a logical and scientific review of available information and forms the basis for preliminary discussions with regulatory agencies. Although performing a gap analysis might seem overwhelming, it avoids a lot of pain by creating a good plan and troubleshooting concerns before they become issues. It is also a comfort-building exercise, not only for the developers but also for the regulatory agencies since it gives an unbiased analysis of the current status of development and studies proposed to meet regulatory requirements. While experts will argue the statistics for levels and trends for new biomedical product approvals, all would agree that systematic strategic planning improves the success and progress of potential biomedical products.

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