Resource Allocation in Candidate Drug Funding

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The United States pharmaceutical industry is a titanic economic force, and a hugely important element of civil service, generating $207 Million of annual revenue and providing the drugs used to provide care for 70% of Americans. In an industry of this scale, relatively minor inefficiencies can lead to the loss of millions of dollars, or delay cures that could help countless numbers of patients. In an effort to ensure that pharmaceutical companies operate as smoothly as possible, a logical course of action would be to apply the techniques of operations research on this field. However, the discipline of operations research and the elements of the industry vary widely in topic and purpose. In order to conduct a beneficial and specific analysis, we must narrow both our methodology and our subject matter. The pharmaceutical industry, like all billion-dollar industries, has a range of processes including research and development, production, marketing, sales, and many more. One such process captures many of the unique elements of this particular industry, the development of candidate drugs, and we will concentrate our efforts on developing techniques to maximize efficiency in this regard.

Drug development is the lifeblood of the pharmaceutical industry. New drugs are the industry's equivalent of new products: they cost money to develop, have value as potential revenue sources, and contribute substantially to a company's public image and stock price. The fundamental problem for the companies then, is to choose which drugs to develop with their limited resources, in order to get the most value possible from the selected drugs. As such, a fitting initial approach would be to assign a projected value and cost to each candidate drug, and optimize total value while remaining within the confines of a budget constraint. This naïve initial approach should seems familiar, as it is virtually identical to the classic problem knapsack problem, where one maximizes the value of a set of objects and ensures that the weight of the

selected objects remains below a bound. However, the problem of the pharmaceutical companies is not as simple as mapping their costs and values onto the classic problem. The intrigue of our problem lies not in the basic structure of the problem, but in the unique industry factors that drug manufacturers must deal with. There is a wide range of reasons that a simple knapsack problem cannot sufficiently represent or solve a pharmaceutical company's problem, so our model must include several critical modifications from the original.

The first critical difference between the pharmaceutical industry and others lies in the fact that once a company fully develops a drug, that drug falls under the protection of some very strong patents. Conventional economic and game theory models often use "widgets" as the products on the market, and these models often assume that these "widgets" are easily copied in a competitive market. These assumptions often lead to results that prioritize production capacity and efficiency in order to drive down the costs of similar goods. In our model, we will need to operate under different assumptions. Once a drug has been discovered and cleared by the Food and Drug Administration (FDA), the developing company has the exclusive right to manufacture and sell this drug for the next 15 years. Additionally, over the 15 protected years of monopoly production, the costs of manufacturing the drug are relatively small when compared to the costs incurred in development. Couple this with the fact that healthcare is among the most price inelastic industries in the world, and we see that operating costs of developed drugs should not be a primary concern with our model. In fact, the initial capital requirements to develop a drug far outweigh the operating costs of producing that developed drug. Thus, our model must accurately represent both concerns with high development costs and a long-term view of revenue.

An additional concern that our model must address is the non-linearity of drug development. In a classic knapsack with multiple copies of the same object, if you are willing to take on the weight of twice as many copies, you get twice the value. Drug development, however, operates on a probability basis, and doubling the funding on a project does not double the probability of successful development. Developing drugs requires equipment, personnel, and test subjects, all of which require an initial level of capital to acquire. Therefore, some level of funding below the required threshold does not create any positive probability of development. (If a company only pays for the equipment, and has no money to pay researchers, they have not increased the likelihood of developing a drug). On the other side, spending higher and higher amounts of money on a project will only create decreasing marginal returns. This is why a company will fund several different drugs for the same problem, instead of concentrating the funding on one effort. As such, there is a limited range that matches the purpose of our question, one in which spending any money creates a positive probability, and spending more money increases the probability. As an additional complication, the relationship between funding levels in this range and probability of development is not a linear one. Therefore, we must restrict our inputs to the relevant range, and develop a methodology to map particular funding levels to particular probabilities, without making use of the computationally simple linear mapping.

Another industry factor is both problematic for our model and discouraging for the pharmaceutical industry; developing drugs is a consistently losing proposition. Fewer than one in eight fully funded projects make their way to FDA approval and release. This seems to have a limited impact on the mathematics of the model, which compares the probabilities as numbers

alone. However, our model must also factor in the preferences of the drug companies. A model that takes the product of projected revenue and probability of development to create expected value may not fully capture the intricacies of the industry, particularly because the probabilities are so low. A simple, one player example from game theory demonstrates how equal expected value does not imply equal preference. When faced with the option to win $50 with 100% probability, or win $100 with 50% probability, subjects generally choose the safer, guaranteed $50 payout. Our model must be able to account for similar risk aversion, and create the option of preferring a relatively small payout with higher probability to a riskier alternative with similar expected value.

Our final industry factor to consider comes from the two roles that pharmaceutical companies fill: simultaneously profit seeking corporations and key contributors to the cause of public health. Our naïve model selects candidate drugs to fund with the sole intention of maximizing the monetary profit from these drugs. What happens, then, if a drug company wants to maximize the amount of people it helps? Or the amount of good press they receive? Or some combination of these interests? Curing a particular rampant illness may not always be the most profitable venture, but many companies choose to pursue these causes for other reasons. Recent instances of price gouging in the industry have created intense backlash, and provide a clear reminder that drug companies may not be best served by focusing on profit alone. As such, we must consider a metric that measures the hidden benefits of a drug, and modify our model to allow a company to be interested in more than just the revenue a product can create.

The first and perhaps most important element of our model is the data that powers our calculations. As such, an examination of our data sources is necessary to demonstrate the accuracy and realism of the hypothetical data sets our model will operate on. In creating our model for these candidate drugs, we researched important resources for funding clinical trials in order to understand the magnitude of the costs associated with these projects. Furthermore, we needed an accurate way to represent the probabilities of different hypothetical drugs being passed through each stage.

Our first step in data discovery involved examining the business processes and budget development of clinical trials. This first source of funding is not one likely to be thought of as a significant part of funding: research subjects. “Research subjects are the most highly prized commodities in the clinical trials industry” ("Bookbinder"). Most of the costs and difficulties in clinical trials are tied to research subjects, especially if the drug negatively affects the patient. Additionally, each trial on a subject could be worth thousands of dollars. Finally, there are costs associated with paying doctors to select patients for these trials and monitoring them throughout the process. Consequently, many patients receive sponsors for these trials. Sponsors usually donate a specific amount per patient or just a specific amount and ask that the company work within that budget.

As an alternative to doctors, many pharmaceutical companies are starting to use contract research organizations (CROs). CROs are typically significantly cheaper than doctors are, and help to break down “the process into discrete, narrow steps” (Bookbinder). This helps to maximize efficiency, while also helping find research subjects. Unfortunately, CROs are not without scandal, as their attempts to make the clinical trial process more efficient can cause

some critical steps to be overlooked, which can create problems. However, speaking strictly in terms of lower costs, CROs are the cheaper route.

The second major source for funding candidate drugs is company revenue. Big pharmaceutical companies such as Pfizer, Merck and Johnson & Johnson typically derive significant sources of income in the form of popular over-the-counter drugs, prescription drugs, or self-care products. For example, Pfizer has a whole section in their budget dedicated to the revenues of their major products, which are millions of dollars.

Having identified the two predominant funding sources for drug development, we must also acknowledge the expenses that go into funding for clinical trials. One significant expense for all trials that appears in every phase of the clinical trial process is FDA approval to continue developing a drug. The process of receiving approval from the FDA is a long and costly one, which contributes significantly to the low probability of a final product coming to fruition. In addition to the usual expenses such as facilities and administrative costs, FDA fees, materials, shipping and specialty equipment costs, another large expense is patient litigation. In performing clinical trials, most drugs are tested on animals before proceeding to human trials. However, as with most significant projects, there is still a possibility that things will go wrong. Consequently, patients may take legal action against the developers if they are negatively impacted by the trial, at significant cost to the companies.

Analyzing the funding sources and expenses that drive clinical trials was a major step in the formation of our model. They helped us understand the extent to which drugs are funded, and the important factors to take into consideration when looking at the limitations and scope of our problem. Obviously, our model must reduce the complexity to focus on the probabilities

of candidate drugs being funded. However, we felt that the scope of these funding sources and expenses are greatly covered by the probabilities we used for each phase of the clinical trial.

The probabilities we used came from "Research and Development Project Valuation and Licensing Negotiations at Phytopharm plc." In this article, the authors examine the projects of a specific company in the United Kingdom. Specifically, they evaluate methods that are used, decisions that are made, and the value of their projects. This research illuminates the pharmaceutical and food development process and the highlights typical routes to the market, but what caught our attention was Table 1, which gave the probabilities of moving to the next phase of clinical trials of typical drugs by pharmaceutical companies. It is interesting and beneficial to note that the smallest probability is moving past the Basic Research phase. This is because thousands of compounds that can be introduced in a given venture, but only one will ultimately be used and developed even further to create a new drug ("Project Valuation and Licensing Negotiations at Phytopharm plc").

Phase	Typical duration (years)	Probability of advancing to next stage (%)	Probability of FDA approval (%)	Proportion of total R&D costs (including failed products) (%)
Basic research	2	0.2	0.01	24
Preclinical	3	50	5	12
Clinical I, II, and III	6	12.5	10	29
FDA review	1–2	80	80	35

Table 1: The typical pharmaceutical development and review process takes many years and carries a high risk of failure.

The above table gives the probability of moving on to each general stage of a clinical trial, including the probability of FDA approval for typical drugs. This table makes up the basic template for our model, but our research expands upon it through by the magnitude of the funding levels for each drug.

Through our sources for funding, expenses and probabilities, we were able to start forming our model for the allocation of resources for candidate drugs. Before going forward with any model for maximizing profit from drug development, we had to decide on how to address the unique factors of the pharmaceutical industry that vastly increase the complexity of the modeling problem. Finding participants for clinical trials can be a challenging process and potentially stall the progression of drug development. However, for the sake of simplicity we decided to assume that each of the drugs that our model is choosing between for development has no shortage of participants for studies. Another factor to consider is that the profitability of a drug depends on drug type. A new cure for a disease would be groundbreaking and rake in the revenue, but another over the counter cough suppressant will probably have a very low return on investment since the market for such drugs is already saturated. Because interaction with other drugs complicates the decision making process for our knapsack problem, we decided to assume that the chance that a certain drug in development is profitable is independent from all other drugs also being considered for development and those currently at market.

Armed with our assumptions, we built our model variables by closely adhering to the table on page 6 with one significant adjustment. The table provides two separate probability values for a given drug in development. The first is the chance that a drug makes it to each stage of development given a funding level, and the second is the chance that the drug obtains FDA approval at each stage of development. Ultimately, drugs cannot be available on the market in the United States without FDA approval; in other words, without federal approval developed drugs cannot earn a company profit. Seeing as FDA approval is the main bottleneck

in development, we decided to define the probability of success for a given drug at a given level of funding to be equivalent to the joint chance that it passes onto the next stage of development and obtains approval from the government. We decided to maintain the discrete funding levels as shown in the table because drug funding is not a continuous process; a certain amount must be allocated by a given time in order to obtain researchers, facilities, materials, legal help, and so forth.

As mentioned before, we decided to approach this problem of optimal allocation of resources for candidate drugs by solving the knapsack problem of choosing a set of drugs that maximizes optimality subject to resource constraints. More specifically, we seek to maximize the expected value of the profitability of a drug given a level of funding. By profit, we are using the accounting definition of revenue less expenses. The inputs for our model are revenue, expenses, and probabilities of success. Revenue is entirely dependent on the drug making it through every stage of development since we cannot sell an unfinished drug. Thus, the model takes projected revenue as the value input for each drug. In addition, since successful drug patents last for many years at a time, the revenue amount is the amortized total value of the drug over its lifetime per year. Expenses occur at each stage of development, (a certain level of funding is required at each stage), and so these values are provided to the model for each drug for each stage of development. Funding levels are provided per drug per stage of development along with associated probabilities of success. We define each drug as an indicator variable, taking the value 1 if it is chosen for development and 0 if not chosen. Our model takes the following as inputs:

- set of drugs $\{d_1, d_2, d_3, \ldots, d_n\}$

- proposed yearly profits per drug: $\{r_1, r_2, \ldots, r_n\}$
- sets of (funding levels, *P*(success | funding level)) per drug per stage of development: $f_{i,j} = \{ (l_{i,j}, p_{i,j}) : \forall i \in \{1, \ldots, n\}, \forall j \in \{1, 2, 3, 4\} \}$
- lump sum value for overall budget constraint BC, that is the entire R&D department's budget for that year

Given all of these values, our model is as follows:

$$MAX_{ij}\ E\ [d_i(r_i - f_{ij})]$$

$$\text{subject to } \sum_i \sum_j f_{ij} \leq BC$$

We projected values for each of the above inputs based off the Pfizer budget information that we had researched and loaded this information into a csv file. We then solved the above knapsack problem by using a dynamic programming approach. At the end of running our Python script, we obtain the optimal expected profitability and the drugs chosen to be developed.

This model can be expanded with moderate ease in the scope of this project. For example, we can tackle the problem of balancing profit and societal obligation by adding a societal value option for each drug. If we look at the yearly Flu Vaccine for example, it is usually given away for free, but has an incredible societal value in keeping the population healthy. A drug that is able to cure a common form of breast cancer however, would have both huge profitable and societal value. In order to incorporate this into the model, each drug was given two values, and an input was given for the balance between the two. Therefore, if a company put a 60% importance on the societal value, the expected payoff would be 40% of the profit value, and 60% of the societal value.

In addition to this complication, we hypothesized that drug companies might be risk averse or risk seeking. Thus, a company that is risk averse would opt for a drug with a higher probability of making it to the market, even if it has a lower payout than a slightly more risky drug. To incorporate this into our model, we place an exponent on the probabilities that the drugs are able to get to market. A higher exponent would mean a more risk averse firm, and makes smaller probabilities reduce at a much greater rate than something above one half. For future research, this could be the economic risk aversion derived from a person or company's utility function.

In future research in this field, there are many ways that we could add elements this model. One for example could be more specific budget constraints contingent on the drug being produced and the equipment and researchers necessary to create the drug. Required numbers of trial patients, payment steps in FDA approval, and scheduling when drugs go through particular phases and how they affect stock price of the company could be explored as well. If a company has a risky drug and a safer drug on a similar timeline, it might hold the stock price more stable than getting the safe drug approved for the next stage and the risky drug failing badly a few weeks later.

There are many different ways to go about creating a drug development strategy for a company. A driving factor in the diversity of these strategies is the wide range of priorities that executives can have while steering their companies. This diversity inspires both the simple computational roots of our model, and the ability to customize which elements are maximized in the objective function. The fundamental problem of pharmaceutical companies is not a particularly novel one, but each player in the industry has unique desires, and molding a

universal model to represent this is an ideal way to help each company operate more efficiently.

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