4E12 Project Management / Lent 2024

Individual Coursework Assignment

Read the following case and respond to the following questions:

Assignment Questions

1. Which of the project portfolio options currently facing CBS do you favor? Specifically, which two projects would you advance in development? What would you do with the rest? Please justify your portfolio choice by explaining the criteria and the rationale for your decision.

2. What other information, if any, would have been useful to have before making the decisions above ?

3. In general, what management systems and processes should a company (not just CBS) have to make good decisions like this ?

4. How would you incentivize the development teams for the projects you decided to fund?

Submission Instructions

• Your report should be no longer than 3 pages (single-spaced, 12 font size, excluding any figures/appendices which are optional).

• It is up to you decide how to allocate the space among the questions, but I would suggest that each question gets at least half page and questions 2-4 no more than one page.

In November 2019, Katherine Scott, CEO of Cambridge Breakthrough Science (CBS) had an important decision to make: the company currently had four promising candidates under development, but it was unlikely that the company could fund more than two of them for subsequent development.

The decision was far from trivial as each project had its own strengths and weaknesses, and various stakeholders in favour or against it. The company should also decide what to do with the two projects that would not receive immediate funding. One option was to hold those projects as backups in case the selected ones failed. Another option was to license those projects in other pharmaceutical organisations for considerable licensing fees (upfront plus milestone payments)

The Pharmaceutical Industry

One unique feature of the pharmaceutical industry is that regulatory agencies -such as the Food and Drug Administration (FDA) in the U.S.A. and the European Medicines Agency (EMA) in Europe- closely oversee the drug development process. Before testing in humans is permitted, "preclinical trials" have to show sufficient evidence of safety to gain FDA/EMA approval for an Investigational New Drug Application (IND). Testing then proceeds through three phases with humans. Phase I focuses on safety; Phase II on effectiveness against designated diseases and Phase III is large-scale testing with the doses to be prescribed when the product is sold commercially. This process is notoriously long, risky and astronomically expensive: from initial concept to commercialization, it takes on average 12 years, often more than that. Even if a drug makes it to human testing it only has an approximately 10% chance that it will ever make it to the market, and that is why the most recent estimates put the average development cost of a drug to $1.4 billion dollars (a figure that includes the 90% of times that development efforts fail).[1]

CBS Pharmaceuticals

CBS was founded in 2007, so it was considerably younger (and smaller) than most pharmaceutical firms in the industry. Despite its small size and an annual R&D budget that was a fraction of the key industry players ($300 million compared to $5-8 billion of big pharma), the company had great ambitions. In fact, CBS's management believed that precisely because of its small size it had an advantage in terms of speed and agility, and therefore, it could be much more productive and innovative than its much bigger competitors.

From its inception, CBS's mantra was "science first, the rest follows". As in every company, some key executives had the final say in key decisions. Yet, in the case of CBS the scientists

[1] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics*. 2016; 47:20–33.

involved in the projects provided considerable input and senior management tried to encourage constant and reliable communication between the different levels of decision-making. As such, lack of engagement and involved was hardly ever the case at CBS. Different points of view were not only allowed, but also encouraged.

Scott was a strong advocate of such diversity in opinions, even when some of them were not aligned with her personal views. Being a passionate scientist herself, she believed that an essential part of the drug development process is people who are excited about the projects they work on. In fact, the first product of CBS that made it to the market, was a project that originally the senior management (including Scott) decided to abandon. Despite that decision, a small group of scientists worked in late evenings and weekends, until they were able to produce sufficient evidence to turn around that decision.

CBS was, so far, a company focused on early-stage research and drug discovery, rather than late-stage development and commercialization. CBS's strategy has been to produce drug candidates in different therapeutic areas, and the decision whether to pursue a candidate in one therapeutic area versus another was entirely driven by the technological potential of a molecule. CBS's management believed that this freedom to select the "best candidate" gave it an advantage over other companies that often made selection decisions based on their existing infrastructure or their sales forces size in a given therapeutic area.

In the 12 years CBS had been in business, it had succeeded in getting two of its drug candidates approved by the FDA and into the marketplace. In both cases, the drug candidates had been licensed to large pharmaceutical companies that had incurred the large late-stage development costs. The reward for CBS had been substantial upfront and milestone payments, along with royalties (paid as a percentage of drug sales). Given the long development cycles of the industry, having originated two drugs that made it to the market during its short history was definitely impressive. Yet, market analysts kept iterating that they would like to see more late-stage candidates. According to the head of R&D, however, there was a very clear explanation as to why this was particularly challenging for CBS: "At CBS, we have decided to go after the most difficult and novel projects. That inevitably means that only a very small fraction of them would make it to late-stage development"

Given its size and the astronomical costs of the drug development process, CBS's strategy was to choose partners with complementary strengths to advance the drug candidates that could not be developed internally. Such alliances offered the much-needed financial support, but also critical skills that needed to bring a drug to the market such as manufacturing, marketing and sales expertise. At the same, in most cases out-licensing a drug candidate meant that CBS had no longer control over the development pathway. Even in those cases were CBS and the partner were jointly developing the drug, the collaboration was not always smooth as different firms often have different priorities. A key concern of smaller companies is often that the larger partner might deprioritize their key compounds. Clearly, the amount of financial support and

in general resources that a partner was willing to commit varied substantially. According to CBS's business development head, big pharma right now wanted to see strong clinical data to get excited about a candidate.

CBS's CFO noted that also seemed to be the case with the capital markets. Raising capital in public markets seemed to be more challenging for biopharma companies than previous years. Investors seemed to have a preference for late-stage assets rather than early candidates that promised blockbuster returns. Taken together, that meant that it was unlikely that CBS could raise the capital needed to maintain its broad research portfolio and also build commercial operations. Given its commitment to proceed with the latter, some scale back was needed for the former.

The Portfolio Candidates

Four candidates were thought to be the most promising: RP-A, RP-B, RP-C, and RP-D. The company had decided that it held sufficient resources to develop only two candidates on its own.

RP-A

RP-A was a molecule that inhibited an enzyme (enzA) in the body that was believed to play an important role in the regulation of immune system activity. As a result, RP-A had the potential to treat a number of important diseases. enzA was also a "validated target" meaning there were already drugs on the market known to affect enzA. Even CBS had other enzA inhibitors in development besides RP-A. Still, RP-A was considered by many in the company to be the most promising candidate in this group of drug candidates.

RP-A had plenty of other proponents at CBS, especially since it was the candidate that, if successful, would get CBS to the market the quickest (RP-A was the most advanced among the four candidates). At the same time, other executives note that it had the least "scientific sizzle" of all the candidates as it lacks a novel mechanism, and many scientists see it as a "me-too" drug. In fact, for the primary indications, there are already drugs on the market. Despite these downsides, several executives noted that successfully launching a product in this industry is so rare, that a company like CBS couldn't afford to abandon a project simply because it lacked scientific excitement.

RP-B

RP-B was an inhibitor of an enzyme called enzB. EnzB believed to be associated with the onset and progression of inflammation. In June of 2017, CBS began Phase I clinical testing of RP-B. Testing showed that the drug was well-tolerated in patients and had an excellent

pharmacokinetic and pharmacodynamic profile. CBS was currently testing RP-B in a Phase IIa pilot study designed to evaluate the safety and tolerability of RP-B for a specific disease.

RP-B had several supporters within CBS. One executive noted: "It's a great drug and easy to make. Seventy percent of the drug stays in your system for therapeutically attractive periods. The side effects are manageable." Since inflammation was responsible for a wide range of diseases, RP-B had the potential to be tested in multiple indications.

Another executive stressed the strong commercial potential of PR-B: It's an oral drug in a field of injectables. Right now, very few oral meds are covered by US Medicare but, if the prescription drug benefit bill passes, oral drugs could be covered under this legislation. We are currently in Phase II, looking for efficacy signals. One concern was that similar drugs seemed prone to toxicity issues. Several companies had tried developing enzB drugs, and most had failed.

RP-C

RP-C was a drug that inhibited an enzyme called enzC. EnzC believed to play an important role in a number of chronic inflammatory diseases. Success with RP-C could provide a breakout opportunity for the company. According to an executive: "Everyone is excited about RP-C. Success with RP-C on our own could launch CBS out of low orbit." Another executive added: “RP-C uses proprietary chemistry. We have a strong patent position in this area—there are no other enzC inhibitor candidates on the market right now. If enzC inhibitors work, it could be a blockbuster opportunity."

By August of 2017, RP-C had started Phase I testing after successfully completing the preclinical stage. While RP-C was fully owned by CBS, it was also a "second-generation" compound to another CBS-originated drug, RP-O, an earlier enzC inhibitor being developed through a partnership with PharmaCo. RP-O was nearing completion of Phase II trials in both RA and OA. RP-C was chemically distinct from RP-O, giving CBS full rights over the compound. However, under a licensing agreement with PharmaCo, if CBS decided to go ahead with the development of another enzC inhibitor, it would have reduced influence on certain committees governing the development of RP-O, lose rights to a subsidized sales force in U.S./Europe, and sacrifice certain financial benefits of copromotion. RP-C's relatively high manufacturing costs (at this stage of development) were another point to consider.

RP-D

RP-D was being investigated by CBS as a novel small-molecule inhibitor for an entirely new class of enzymes. The molecule, which entered preclinical tests in 2018, had shown potent properties as an inhibitor of a protease enzyme believed to be essential for viral replication of a critical disease. Furthermore, current treatments for the disease were only effective in

roughly 30% to 50% of chronically ill patients. Most of these treatments were associated with significant side effects, and none was a direct antiviral therapy.

In November 2019, RP-D was still in preclinical studies, with expectations to begin Phase I trials in mid 2020. While this made RP-D the least developed of all the portfolio candidates, the program executive in charge of RP-D, described the attractiveness of the candidate: RP-D is potentially a billion-dollar drug. There exist large unmet medical needs in this area—current medicines are suboptimal. CBS has a leadership position in this area, potentially best in class. RP-D was also a premier example of CBS's ability to do rational drug design and caused plenty of excitement within the company. "RP-D has the right concept—we believe it will work," said Scott. Another advantage, from a commercial standpoint, was that CBS could sell the drug to doctors using a specialty sales force.

On the other hand, RP-D was complex and costly to make with substantial testing and development costs. Some people in the company thought it better to find a partner with deeper pockets to help with the compound's development. Also, a decreasing number of new infections made this area a time-sensitive market, and even optimistic expectations put RP-D reaching the market in 2026. CBS management knew it could not wait long on this opportunity.

The Portfolio Decision Criteria

The challenge for CBS was to compare drug candidates at different stages of development, with different technical properties and different potential therapeutic applications. Just like its approach to drug discovery, CBS preferred to look at the problem from several angles.

CBS used risk-adjusted Net Present Value (r-NPV) as part of its analysis of each candidate's potential. r-NPV took into consideration the expected cost and risk of each drug's clinical development as well as the estimated commercial value of the drug upon being approved and reaching the market. As a result, management was able to produce a rough measure of the value of each candidate, as an investment opportunity, in present-dollar terms.

While r-NPV and other valuation techniques provided the ability to compare different drug candidates as investments, CBS management knew such methods were far from exact measurements and questioned how much they could be relied upon. One executive noted: “r-NPV models are more valid for late-stage development compounds, when you have a pretty good feeling of the potential market ahead in one or two years. Everything else is pure speculation. For us to predict r-NPV 10 years out gives us a nice number, but it's not terribly meaningful. For me, the importance of the models is in facilitating the conversation, getting the questions out, and helping interdisciplinary conversation.”

The chief scientific officer talked about the risk attributes of the different candidates and the trade-offs involved with choosing two: “The enzA mechanism is already a selling product. Therefore, RP-A has low mechanism risk. On the other hand, RP-B and RP-C have new

mechanisms with more unknowns. RP-C and RP-D both have novel targets. Choosing a follow-on drug, such as RP-A, you may know the molecule works, but you are facing a possible land war once the drug is approved. Alternatively, choosing a new drug is more risky in the beginning, but you have less competition in the marketplace. Choosing candidates in the same therapeutic area causes correlated risks and returns. However, different therapeutic areas require multiple sales forces. RP-B and RP-C have overlapping therapeutic areas. Together, RP-D and RP-C have similar risks and put a lot of pressure on new infrastructure. Also, it could take the longest to get to market."

Some people at CBS thought the company should work on minimizing certain kinds of risk. These being the first two drugs CBS would develop by itself, they would have a large impact on the company's growth and organizational learning. According to a marketing executive, "First and foremost, which drug is most likely to make it onto the market? We should favor drug candidates with lower technical risk, even if their sales potential is lower." The senior vice president of drug evaluation and approval, agreed: "We don't want to choose a compound that fails and has to be pulled from the clinic in the next six months. . . it would have a serious impact on the organisation's momentum."

CBS management knew that their employees were driven by the opportunity to solve important medical problems. The scientific reputation of a drug and the disease it treated had a strong influence on CBS scientists' preferences for candidates. Getting a drug to market would require a great deal of effort throughout the organization, and therefore, it was in CBS's best interest to pick candidates its scientists were motivated to work on.

The head of R&D discussed how the scientific novelty of a drug program and the medical need it targeted influenced the portfolio decision: "Having medical impact is important when picking a candidate. Sometimes medical impact is indeed highly correlated with commercial success, but not always. There are many examples of drugs that made lots of money, but without necessarily offering a medical breakthrough. "

Katherine Scott reflected on the status of the programs and knew that a final decision would have to be made soon. She was well aware that stock market analysts on both sides of the Atlantic, as well as company insiders, were closely following the company's actions. One thing was for sure in her mind: CBS was a "serious" drug company, as she noted: "We go after serious drugs for serious diseases, not wrinkle creams."

Exhibit 1

CBS's Input assumptions for the r-NPV Analysis

	Probabilities of Success						
	Phase I	**Phase II**	**Phase III**	**FDA Approval**		**Total Revenue**	**Manufacturing Costs**
RP-A	1	0.6	0.65	0.75		1000	50
RP-B	1	0.65	0.5	0.5		1500	100
RP-C	0.8	0.7	0.6	0.8		1200	150
RP-D	0.5	0.45	0.7	0.6		2000	200
Avg. cost	15	24	86				

Note 1: All monetary values are expressed in present value in millions of dollars, so ignore discounting and any temporal calculations.