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Managing Uncertainty in Biotechnology Firms

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MANAGING UNCERTAINTY IN BIOTECHNOLOGY FIRMS

Introduction

The path from a very early start-up to an established biotechnology firm can be daunting. The small firm faces many tasks associated with funding and starting the business, a myriad of scientific and technology challenges to develop new products, and a long series of changes as the firm adapts and grows to support a commercial product entry into the market. Along the way, a firm's evolution is fraught with uncertainties which can have devastating consequences. Unexpected results from a study, the untimely end of a partnership, uncontrolled burn rates, and many unforeseen events can delay or cancel project development, tarnish reputations, restrict future financing, reduce value for investors and lead to the firm's dissolution. Against this backdrop, managers, investors, and scholars are increasingly looking at understanding and managing uncertainty as a key element related to firm evolution and success.

Based on the journey of a small biotechnology firm and numerous observations gained from other projects involving biotechnology firms, this paper offers insights into how biotechnology firms manage uncertainty as they evolve from young start-ups to commercially established firms¹. We find that uncertainty stems from several sources including the science and technology underlying the firm's product, the resources that support the firm, and the firm's ability to execute and bring the product to market. We also discuss several ways that firms can reduce, avoid and make uncertainty irrelevant. *The purpose of this paper is to examine the key sources of uncertainty and identify ways that managers can respond to these uncertainties to successfully evolve their firm from a young start-up to an established firm.*

Executive Summary

For nearly all young organizations, uncertainty arises from many facets of the business including product choices, financial requirements, and the firm's specific ability to execute and bring a product to market. While these sources of uncertainty may be common to many firms, the level of uncertainty that exists for a small biotechnology firm is exacerbated by a lengthy (up to 12-15 year) and costly (up to \$1.2 million) regulatory process, shifting market conditions, and developing scienceⁱⁱ. Due to these factors, less than 10 out of 5000 potential targets succeed to late stage clinical trials, and only 1 in 5 of these are approved by the FDA for commercial launch.

Product uncertainty stems from just how far a firm pushes the envelope with a product's design and other product choices.

Financial uncertainty arises from the need to raise significant amounts of money and involves somewhat idiosyncratic issues and quirks associated with the different sources of capital.

Execution uncertainty is driven by the scientific, technical and process capabilities of the firm and how these are used to develop a product from concept to market.

Uncertainty changes as the firm develops: initially, uncertainty abounds, seemingly coming from any and every direction. However it quickly takes on definition related to the product, the firm's capital needs, and issues of execution. Later, as the firm evolves and grows, there is a second level of definition: *Product uncertainty* divides into uncertainty related to the primary versus other products and the product attributes that determine how a firm

will position itself relative to competition. *Financial uncertainty* develops nuances related to the different sources of capital. *Execution uncertainty* splits into related areas of scientific foundation and the many processes that are needed to bring the product to market.

For a new firm, uncertainty is ubiquitous. However, managers can take several steps to manage uncertainty. These include actions that provide more information and help managers make informed decisions. More importantly managers can also take steps that allow the firm to bypass, circumvent, or make uncertainty irrelevant that firms commonly face. These include:

Planning that focuses on product development.

Prioritizing the uncertainties.

Pacing the firm's development.

Conserving resources.

Communicating with other managers and outside supporters.

Involving individuals with different areas of expertise.

Learning from surprises to gain new insight and adapt to these discoveries.

Sources of Uncertainty

The uncertainty that impacts a biotech company as it evolves from the recognition of an initial idea held by the bio-entrepreneur, to the building of a firm, to the time when a commercialized product gains market success, infiltrates nearly every aspect of the business. Uncertainty exists in the choices of which product or products to go after first, second, or in parallel; in the decisions on which sources to approach for capital, and in the execution of many steps that make up the development of an initial concept into a viable product. This section briefly introduces these different sources of uncertainty.

Product

Uncertainty associated with the product first begins when the firm is formed and individuals begin to take the initial concept of the firm and make product and development choices. In these early times, the choices a firm makes involve complex considerations between various risk-return tradeoffs. Managers must determine “Which attributes will the market value? Are these possible to achieve? Can or will the firm be able to produce these?” “We select an ideal product and then have to wait and see how close to that they can come.”

The uncertainty that a firm faces in relation to its product goes beyond which general product area the firm chooses to enter. It also includes just how far the firm chooses to push the envelope in terms of product design and the number of products it develops. Cutting edge product attributes may command greater market value when the firm begins but after years of potentially difficult development, the market may be quite different. Multiple products theoretically will expand the firm’s potential revenue streams. However, uncertainties arise as to whether the firm can engineer new, unique attributes into the product, what market conditions will exist when the

product reaches market, if one or more of the products do reach the market.

Still, the product choices made early on affect the degree of uncertainty present throughout the development process. Until the FDA approves a product and the market accepts it, “there is tremendous uncertainty as to whether the idea is a winner.”

Financial Capital

The uncertainty related to financial support stems from the timing and source of capital infusions. Where the funds will come from and when the firm will raise the funds are the first questions - and thereafter constant questions - as a young firm gets started and grows. The basis of this uncertainty stems from the fact that capital is critical: “To move ahead you need money, you simply have to raise it.” To raise money, the firm must determine which source – VCs, private investors, government grants (SBIRs), partners, or public markets – is best, given the firm’s specific stage and situation. This consideration is critical because “The different sources have their own shortcomings, their own sensitivities with respect to R&D outcomes.”

After capital is raised, questions still remain. Early on the questions are “Will the initial investors come through again and can additional investors be brought on board? Later the firm must grapple with “Do you go public – and all that involves – or do you raise more private money which dilutes the current investors’ shares? Alternatively, you could also go for a partnership deal – and the uncertainties that brings in – and then go public after that.” Of course, “there are things beyond our control which can happen: the firm might also merge with a company, despite preferences to take the product to market alone.”

Execution Uncertainty

Also critical for a young firm is the need to execute: to conduct tests and perform the steps that develop and protect

the product. But for most young firms, there is uncertainty related to the firm's ability to execute. "Can the firm bring the product to market?" As the product evolves, there is always the question, "Are we doing it? Are we proving the concept? Or, if you make it ... what's it going to look like?" You just never really know."

Execution uncertainty rests on the firm's ability to complete several tasks. The firm must secure the necessary patents, prove the concept, choose and develop the product from its initial ideal to a commercialized product, obtain additional patents to protect current and future intellectual assets, produce the product, scale the production manufacturing into a reliable process that meets all quality standards, design and successfully complete clinical trials to navigate the FDA regulatory process, launch the product and ultimately expand the firm's product offerings, revenues and profits. As the firm evolves, execution is a constant challenge: "you have to wonder if you're going to make it."

The Evolution and Relationships among the Uncertainties

Defining Patterns of Uncertainty

The evolution of uncertainty appears to take on an interesting pattern. Initially uncertainty abounds. It is everywhere: "it is mind-numbing how many things could go wrong and derail the firm."

Later, as the founder and the firm's first employees start to hone in on a specific product concept, the sources of uncertainty begin to take on order. The firm raises capital and financial uncertainty is reduced but product and execution uncertainty enter into prominence: can the firm advance the product along – far enough along – before the money runs out? Will the product work?" The firm begins to conduct tests, amassing data that will ultimately show if the product concept is viable. As results come in, product uncertainty flares in

response to unexpected or disappointing results, while execution uncertainty moves in waves – cresting as the firm begins new activities, but falling as each test is completed.

As time passes, capital runs down and financial uncertainty increases in relation to the need for more cash, even to the extent that product and execution uncertainties are put on hold until financial support is restored. In this sense, financial uncertainty appears to be the constraining element to the firm's evolution. As one individual stated, "money really is time for a small start-up."

Once the firm reaches a certain stage – perhaps as it enters Phase I or II clinical trials - there is a second level of definition within the uncertainties that appears:

- Financial uncertainty breaks into separate uncertainties associated with the different potential sources of capital.
- Execution uncertainty divides into different elements related to the science and the many processes that are needed to bring a product to market.
- Product uncertainty begins to make distinctions based on attribute choices and market conditions.

These areas generate their own uncertainties but also occur simultaneously as the firm develops.

Relationships among Uncertainties

While uncertainty stems from several sources, the sources of uncertainty appear to be interrelated, tightly linked, and re-occurring over the course of a firm's evolution. When the firm first begins, uncertainty is ubiquitous and can be viewed as rising from nearly every possible source. "There are so many things that can go wrong." While definition of the uncertainties occurs over time, the sources of uncertainty rarely act in isolation during the life of the firm. Instead, one type of uncertainty can impact another in both positive and negative ways.

For example, the need for capital and where to get it is a central concern and source of uncertainty for a new firm. At the same time the science behind the product and the ability to engineer desirable and differentiable attributes into the product are also present and intricately linked to financial uncertainty. The financial capital that is raised supports scientific investigations which further develop the product attributes and helps build investor confidence in the company which in-turn helps the firm raise additional capital so the next investigation can be done. "If you start to run out of money, data is not being generated anymore."

Product design choices also influence the potential value-attributes of the product and the attractiveness of the firm which impacts the ability of the firm to raise capital. Product attributes that are chosen by the firm also affect the difficulty – and uncertainty – associated with making the product which in turn affects the resources needed.

To complicate matters, the ability of the firm to raise money is not only affected by the product, but also on the perceived quality of the management team and specifically, their ability to execute. However, the firm's ability to execute rests on individuals and the firm's ability to attract talented people. Attracting the right talent depends on the science, the level of capital funding, the quality of the current employees and the potential financial "upside" for individuals. Potential success rests on the firm's ability to execute many steps in the development of the product to demonstrate the product's success within a strict regulatory environment. Execution is heavily influenced by decisions at the firm and the interactions among individuals at the firm, those at partner firms, outside contractors, and regulators.

While the level of uncertainties may change once the firm successfully launches a product that provides revenues, positive cash flows and then profits that can sustain

the firm, the connections among the uncertainties and the sources of uncertainty remain. To move ahead, the firm works to synchronize the sources of uncertainty such that they form a positively reinforcing cycle. "The thought is that financial uncertainty isn't huge as long as the science appears to be progressing, since if the science progresses and shows that we can engineer the desired features, we can raise money." Positive reinforcement continues as "Constant advances in the product help to raise a steady stream of financing."

Uncertainties can also create a negative reinforcing cycle. A study – due to inconclusive science or poor execution – can produce results which tend to make raising capital more difficult and limit the firm's ability to advance the product. Internally, this can create ripple effects beyond financial uncertainty. Surprises or negative news from a test can trigger a negative cycle that increases uncertainty for the firm on all fronts: product, financial capital, and execution. "Set-backs can play on the scientific team: why can't we do this? I thought we were good at this. Why can't we get this done? Will this product work?"

The links between uncertainties is also apparent in other decisions. For example, there are positive effects when a biotechnology firm partners with another (often larger) firm because it brings both capital and credibility to the biotechnology firm. As a result, both financial uncertainty and execution uncertainty are significantly reduced as the firm takes in capital and leverages its new partner's skills. However, when a partnership fails or terminates even without failure, per se, this too can raise uncertainty levels in all areas. Without the partner, it is likely that a new source of funding is needed. In addition, when a partnership ends, the firm can experience a loss of reputation which raises questions as to the viability of the product and the smaller firm's ability to execute on the product development. After all, "the larger firm

pulled out which signals a failure to the market.”

Additional connections among the uncertainties are also evident. News – good or bad – related to a product also impacts other areas of execution. Since firms often work on several fronts in parallel, bad news on a study related to one product creates stoppage in other areas. When a trial fails, manufacturing ramp-up is put on hold, the courting of future partners pauses and product launch efforts are minimized. Bad news on a central product can put the company into a more reflective, stunned stance. When this happens, uncertainty seems to loom large and a set-back in one area can spark heightened awareness of uncertainties from every source: “What should the company do? Can it execute? Is there evidence to suggest that another attempt is likely to succeed? Does it have, and can it get, enough capital? Where will the firm be in a year? If it makes it, will the Street be benevolent or will the firm need to partner to go ahead? Can the firm get a second product to market?”

These spillover effects - where uncertainty in one area serves as a catalyst for uncertainty in another area and news on one front cascades into other realms - point to the fact that uncertainties are tightly linked. Uncertainty is not a single-source phenomenon. Instead, questions and uncertainties related to one area (capital, product and execution) always produce complex ripple effects that impact other areas.

Managing Uncertainty

Managing uncertainty is often equated with reducing the risk around a potential outcome. To do this, individuals gather information that can help them calculate more certain estimates of outcomes or understand more thoroughly what will produce a desirable outcome. Based on our interviews, we find that

individuals do seek additional information to reduce risk in an attempt to understand more precisely the likelihood that a specific outcome will occur. However, we also find that instead of trying to pin-point the chances that something will happen, individuals and firms can manage uncertainty by taking actions which are not focused on outcomes as much as they are on discovering optimal actions to bypass, circumvent, or make uncertainty irrelevant. There are several steps that individuals take to gather information in order to reduce and overcome uncertainty. Based on our interviews, these include seven interrelated activity areas: planning, prioritizing, pacing, learning, conserving, communicating, and involving.

Planning

While planning can conjure-up an image of a slow, even bureaucratic process that is more synonymous with large organizations, planning can help young biotechnology firms reduce and manage uncertainty as the firm evolves. To benefit a small firm, planning should examine possible outcomes and determine the actions that will contribute to these outcomes. Looking at what might happen and specific actions that will help or hinder those outcomes can allow the firm to build or sharpen its awareness of how actions impact the firm’s goals. By taking the time to formulate options based on likely outcomes, the firm can “put a plan in place while thinking about the impact of actions for likely futures.”

An example of how this type of scenario analysis works involves managing financial uncertainty. Outcomes include not only getting the money or not, but determining realistic valuations, obtaining leads, generating interest, and energizing new advocates that can result in new contacts and future financing. With these multiple outcomes in mind, actions that can work to reduce financial uncertainty include “cultivating multiple sources” of capital and

“raising additional financing whenever the opportunity arises.” The plan to cultivate multiple financial sources reduces the uncertainty around whether capital will come in and whether the right kind of support (e.g. an important partnering deal) will ‘hit’ when it is needed, since the firm has a broader network of potential support. Accepting financing when it’s available – instead of only when it’s needed – also reduces uncertainty; it “allows the firm to have a cushion for unexpected downturns.” It can help to reduce uncertainties associated with changes or surprises. Cash in the bank “reduces the impact of the Street’s view of the firm following adverse news because cash translates into more time for the firm to develop its products and perform.”

In contrast, if the firm didn’t consider and understand the actions that contribute to many possible outcomes it might miss financing opportunities and is more likely to face increased levels of financial uncertainty. It might even miss the opportunity to make financial uncertainty a thing of the past. For example, many small biotechnology firms only go public after partnering with a larger firm. However, “more than half of these deals terminate before Phase II trials. To reduce the uncertainty associated with deals, and protect against the ramifications of a partner leaving, you simply have to raise money at all times and need to find validation on your own. Otherwise you face uncertainty at the whim of the partner.”

Planning potential outcomes and understanding the impact of actions also helps manage other areas of uncertainty. When it comes to product decisions, biotechnology firms must “consider several product options and choose product attributes in light of market realities, patent opportunities or constraints, all the while trying to determine multiple ways to differentiate the firm and the product from the competition.” While making product design decisions, managers need to “keep

future requirements for manufacturing and market conditions in mind and understand the impact of product features on many areas.” This often means that managers must acknowledge that cutting edge product attributes may not be attainable, market conditions can change and the chance of product success is low.

To counter the downside risk associated with a product, many managers believe that “they need to have additional products in mind.” Developing a ‘secondary’ product along side the primary product becomes attractive. But is it? Planning based on the examination of multiple outcomes and actions that are needed to produce them might suggest otherwise. Because biotechnology product development consumes large amounts of capital, managers might justify the second product on the grounds that it is “short term, easily done, and will provide significant revenue stream.” The second product will “help fund the primary product thereby reducing the firm’s financial uncertainty.” “Besides, revenue diversification, it is argued, reduces the risk to the firm’s investors.” But that doesn’t necessarily mean a firm should diversify.

By examining the course of actions that a second product development requires, the firm can discover that diversification doesn’t always make sense. Developing a second product may make the most sense when the development of one product enhances the development of the other. If strong economies of scope and positive spillovers exist, the firm can leverage what is learned in the second product to aid development of the primary product and vice versa.

The risk for small biotechnology firms is that leverage is not achieved and the firm spreads limited resources across multiple products. This can adversely affect the firm’s future fundraising ability and may weaken the firm’s ability to survive. A firm might find itself in the position where, “instead of providing revenue resources,

developing a second product “detracts from the company’s core efforts, diverts managerial attention, and uses resources.”

Another reason that explains why small firms do not always benefit from product diversification is that the easy-to-produce, short-term revenue-generating product often receives limited planning. Without this planning the second product can take on a troublesome life of its own. Individuals become attached to the product convincing the firm to repeatedly commit additional resource, even when red flags indicate the need to terminate an effort. Individuals argue that it needs just “one more go at it.”

To counter this escalation of commitment, the firm needs a strong awareness of the trade-offs among product investment choices. It can also help to remember that “most products fail or succeed in a very different form than originally anticipated.” Managers need to ask whether an additional test on a secondary product will lead to the firm’s success. When does the cost associated with a second product’s development – in terms of managerial attention, firm focus and goal achievement – become detrimental? At what point does the firm pull the plug? By considering the impact of actions on potential outcomes, and putting go/ no-go triggers into place, the firm can take and stop actions to improve its chances of success. The firm can “avoid the uncertainties that arise when secondary products become a distraction and a drain on resources.”

Planning also involves looking at the product development path. Managers can choose to describe a set of tests and plot a decision tree based on study outcomes. However, what is often overlooked but invaluable for managing the uncertainties associated with execution is analysis of why a product won’t work. Young biotechnology firms are heavily engaged in scientific analysis to advance products and show that a product does work. It is at the heart of

developing a new product. However, relatively less effort is focused on product failure: the naysayer view doesn’t easily fit into the enthusiastic, upbeat entrepreneurial climate that is typical of many biotechnology firms.

Investigating why a product won’t work is valuable because it builds awareness of the ‘cons’ or shortcomings of a product. Studies that test product limits can discover faults and identify potential issues, allowing the firm to set a course that avoids major set-backs and prepares the firm for course adjustments. Because of this, conducting tests on product failure can reduce costs and help the firm manage the negative consequences of product uncertainty.

A case in point is the strategy of choosing to make a minor change to an existing “well-known safe therapeutic because it provides a path to reduce product uncertainty.” In these cases, managers often accept what is known without checking the limitations of the entity for the current application. Foregoing a targeted investigation and analysis of why the product won’t work can limit the firm’s ability to adapt if surprises arise. As one manager suggested after his firm was caught off-guard because years of tests and data hadn’t examined a critical issue that affected the firm’s new application which would have exposed when the product would fail, “a firm shouldn’t hesitate to do what you have to do. The risk might be great. It might be detrimental, but you have to do it. You have to answer the questions related to when the product will fail so you can plan how to make the product work.”

Prioritizing

With a million tasks that need to be completed and seemingly unending uncertainties, how should managers address uncertainties? Managers might address issues as they arise or according to the effort needed to resolve the uncertainty. Answering uncertainties in the order that

they appear might be a natural response: like many other activities – tennis for example - you handle each shot as it comes. Tackling an uncertainty based on effort is perhaps a trained response: take care of the 80% and you've made a dramatic change that is likely to get you what you need. Although these approaches may be successfully applied in some areas, these might not be the best responses for dealing with uncertainties that can devastate a company. Instead, prioritizing which uncertainty to deal with first can help to minimize the potential downside of uncertainty.

At the firm level, uncertainties will always involve each of the three areas – financial, product, and execution. Prioritizing them can mimic an inherent ordering that seems to be present: Financial uncertainties are often very high but are markedly reduced and take on more definition each time money is raised. In contrast, both product uncertainty and execution uncertainty are relatively high and, although there might be a small margin of decline overtime, these uncertainties are prominent throughout the development period. Looking closely at this ordering suggests that a lack of capital, the primary cause of financial uncertainty, trumps other actions. For the firm, securing capital is the top priority since execution and product uncertainty are irrelevant without financial support.

Within the firm, day-to-day priorities might be different. For each manager, the source and prominence of an uncertainty varies according to their perspective. Individuals at the very top of the firm have the broadest awareness of uncertainty, often heading up efforts to raise money while managing the interconnections among the uncertainties. In contrast, department managers readily identify uncertainty that stems from or impacts their areas on a daily basis and, while aware, are less specifically concerned with the details of uncertainty from more varied sources.

Given the level and interconnectedness among the sources of uncertainty, is this a problem? Would a team of individuals all focused on the broader picture provide a more comprehensive and effective approach to managing uncertainty? Not always. In fact, our interviews suggest that a domain-specific focus is a strong coping mechanism for the firm that is growing and facing multiple sources of uncertainty. When individuals stay focused on the specific uncertainties they face, each is more effective. The individual who deals with investor relations can work to communicate in ways that reduce uncertainty associated with raising each round of capital. Other managers can focus on product development, manufacturing, deal making, and market issues to reduce the specific uncertainties that arise within these various domains of work. In this way, the individual managers pool their efforts to reduce several (but not all) facets of uncertainties. With oversight and coordination from the CEO and awareness among top managers, the firm can simultaneously address many uncertainties.

Prioritizing also works to direct individuals on what activities ought to receive their attention. This concentrates efforts and keeps the firm from “having too many irons on the fire.” This focus can help the firm refrain from unnecessary actions and keep the firm on track. More importantly, focus that is based on priorities can reduce the firm's exposure to uncertainties and limit the need to manage specific uncertainties. For example, the priorities based on a founding teams' goal to be a discovery company, limits the need to build manufacturing facilities or to develop sales and marketing capabilities. This set of priorities also limits the uncertainties associated with execution and the product. In contrast, a founding team with the goal of building a large company will prioritize actions in other ways to raise money, bring in people, develop the product, raise more

money, bring in additional talent, raise more money, add new products, add more people, .etc. and will face the corresponding uncertainties. As these examples suggest, the priorities held by a firm set a baseline for what the firm will do and how it will consume precious resources. While often not formally documented, these priorities – often stemming from vision held by the CEO and other founders – make a strong imprint on the firm’s development path, the actions the firm takes and the uncertainties the firm will face.

Pacing

As a firm evolves it creates a rhythm of progress based on the timing of actions that it takes. Pacing represents how fast the firm grows, how quickly it completes a study, how quickly it moves along the path that will get the product to market. Pacing matters because those firms that are able to quickly develop products get to the market sooner, spend less time and resources in the development process, and realize greater revenue compared to those that move more slowly.

As a result, managing the pace that a firm takes, and keeping a momentum can help address uncertainty. Pacing helps to reduce uncertainty because it keeps the firm progressing, making it easier to raise funds and continue to develop the product.

As the firm strives to grow it must add resources, add people and execute on different parts of the value chain to bring its product to market. However, developing a product is filled with trade-offs that can affect a firm’s pacing. For the entrepreneurial biotechnology firm, there is a tension between being driven by a sense of urgency and the need to use resources wisely.

One approach to pacing is to execute various activities simultaneously. Parallel development of processes involves a risk in that the company may use significant resources on all fronts – manufacturing scale up and development

tests - only to find later that there is a problem with the test results and the expenses incurred in manufacturing are, therefore, wasted. The opposite tack of a strictly sequential approach also has shortcomings that are manifested in lost time: sequential processing can delay the firm’s market entrance and result in a less competitive position and significant revenue losses.

Pressures to get to market quickly may lead a firm to execute simultaneously on many fronts in order to achieve a rapid pace of development. However, when these pressures are accompanied by high execution uncertainties, the outcome may derail the firm. A more temperate approach to pacing – such as time-lagging tasks across development areas such that there is a slight overlap in activities across areas – may help manage and reduce uncertainty as the firm achieves gains in one area before building on the hope (and confidence) that the gain would be achieved. This moderate approach can help managers “hold the reins on potentially rash and expensive activities.” In addition, since gains are solidified before actions are taken in other areas, it directs individuals as to when activities can begin and thereby reduces uncertainty associated with the timing of execution tasks.

Pacing can also affect and reflect the firm’s ability to execute specific activities, coordinate across different activities, and to make both independent and dependent adjustment when such shifts are needed. For example, taking a measured pace may allow close monitoring of a clinical trial – which takes some effort and time – but which can also help a firm spot and make needed adjustments. Moving too quickly, a firm may “miss seemingly minor red flags” that turn out to have significant consequences. Therefore while it may appear that the firm could move along more quickly, the benefit of taking a measured approach is that the firm is able to adjust (if needed) which can, in the end,

reduce the overall time between start-up to product commercialization.

To find the right pacing that speeds the product to market, uses resources efficiently and retains a balance between urgency and caution, managers must build an understanding of the cost/ benefit trade-off and the time associated with different activities. In addition, it is critical that managers keep in mind that most products fail. With this in mind, the firm can pull the plug on marginal activities in order to maintain a forward momentum and create a development cadence that retains “the sense of urgency that is critical for moving the product along” while maximizing resource utility.

Conserving

For small start-up firms with limited resources, conserving resources is one way to reduce uncertainty. Spending less money by limiting the number of employees, managing to tight budgets, or making smaller, incremental or smarter purchases reduces uncertainty because it stretches the firm’s capital. More capital equates to more time. In the small start-up firm, where the product, finances, and execution contain big unknowns, time is the elixir that must sustain the firm.

Conserving, however, applies to more than finances. To develop and bring a product to market many practices can reduce product and execution uncertainties. The choice of one test over another can determine whether test results answer the right scientific questions and generate the data needed for regulatory approval. How might a firm optimize its choice of tests? In some instances, the best path is to simply follow others. The firm can “use existing and accepted *in-vitro* and *in-vivo* models when these meet FDA requirements.” This path requires little creative energy and “can build the FDA’s confidence in the product.” Rather than constructing a new test and working to gain its acceptance with the FDA, the firm can opt to “take a scientific

approach that is fairly standard in terms of the tests and protocols used for answering some questions. The results can be black and white and clearly meet or fail to meet necessary hurdles.” By following standard protocols, the firm conserves time, money and attention and reduces the uncertainty it faces.

In other instances, a firm must invent the test *de novo* and devise new approaches. Developing these new procedures increase the uncertainty related to the results and the FDA’s acceptance. To reduce uncertainty in these cases, “It is customary that the firm will talk with the FDA about the test, present the logic, and then wait for the FDA’s response.” However, “during this process there is uncertainty as to whether the approach is acceptable and will meet necessary requirements. There is the question of whether the FDA will adhere to the plan or raise new issues once a test is complete.” Unique product design attributes are likely to mean that the firm will need to blaze a path in some areas. When possible, following the lead of others allows the firm to conserve assets and reduce uncertainties associated with execution.

Communicating

A common tool for reducing uncertainty is to gather more information. In addition to getting information, a critical practice that can help reduce the level of uncertainty and help the firm enact optimal activities in the face of uncertainty is giving information by communicating with others.

Communication occurs both internally and externally. Externally, the information that is communicated must be “honest, realistic and temperate.” From the initial start-up to maturity, “it is imperative that the firm manages the message it gives to the outside world.” When the firm is young this information is “honest, but also contains hope and promise.” When the firm is publicly held, the information is “accurate, complete, and transparent.”

Communication that supplies genuine intentions and information reduces uncertainty because it provides a true picture of the firm. When the firm performs to this picture, the communication is validated and the firm gains a reputation for being reliable. This in turn can increase the firm's ability to raise capital.

It is not surprising that a confident and charismatic entrepreneur can over-promise on what a firm can deliver. Flush with excitement, confident in one's team and concerned about the need to raise outside capital can lead to optimistic portrayals of the firm. Indeed, talking-up a company's ability is often thought to be what builds interest and brings in capital. However, speaking beyond the realities of the firm can also serve to increase uncertainty. For example, when investors are brought aboard based on an unrealistic future (e.g. when the time it'll take to get to the next stage is down-played), retaining them as investors in future rounds becomes more difficult, thereby increasing the uncertainty the firm faces.

When communication overstates what the firm can do, it can backfire. As one manager described a situation, "things just fell apart and we all lost a lot because the CEO didn't communicate realistic goals and didn't manage the relationship with investors. Ultimately it crippled the firm." In contrast, communication that is honest, accurate and complete can help to avoid the extra uncertainty associated with finding more investors and the harsh consequences when funds run short and investors can't be found.

Managing the exchange of information within the firm is also extremely critical to addressing uncertainty. The type of internally communicated information that goes the farthest to manage or avoid uncertainty is that which is truthful, opinionated, and open-ended. "Open communication can help individuals understand the various areas of execution that are affected by their actions." Such

exchanges and the mechanisms that encourage open exchanges – including "limited levels of management, face-to-face and personal conversations, respect for differences of opinions, a willingness to speak openly, a norm to listen and a non-threatening environment" - can help individuals pass information that is critical for making informed decisions.

An often overlooked area of the internal flow of information is opinions. In most firms, it is common that internal communication is based on indisputable data-based evidence and conclusions. However, with the uncertainty that surrounds biotechnology product development it is equally important that "individuals talk from their gut, express what they believe and say what they feel." These facets of the communication can represent significant pieces of information that help guide the firm through uncertainty.

To encourage the exchange and genuine consideration of hunches and gut feelings, the firm must build norms that encourage these exchanges without the threat of repercussions. Opinions and gut feelings are all part of the communication that can help firms manage uncertainty as their firm evolves. When included in discussions, these insights can be used along side data-driven knowledge so that a firm can make fully informed decisions. "For the best ideas to reach the surface, people need to be able and be determined to make their points, even when the evidence doesn't point to a single choice."

Involving

Another important tactic for reducing and managing uncertainty is to involve others. Whether the company is looking for financing, choosing a product or working to execute any number of tasks, when individuals with different types of expertise are involved in the processes, it helps to reduce uncertainty. The involvement of a range of individuals lends itself to rich discussions on issues ranging from product

choices such as “potential compounds, the pros and cons of those, the indications that might utilize the compounds, manufacturing decisions and clinical designs.” Such discussions help to strengthen decisions and allow for individuals to present different perspectives and ideas. “Whether the issue is one of business or science, involving a wide array of individuals can ensure that critical knowledge from all areas is taken into account.”

The practice of involving others extends beyond the boundaries of the firm to include partners, the FDA, manufacturers, CROs, experienced consultants, and key parties that play a critical role in bringing the product to market. When the firm involves a partner, it helps to reduce financial uncertainty and can also impact execution uncertainty as the partner’s capabilities and resources are leveraged. (It can also add uncertainty if the firm is dependent on the partner for capital and validation.) Involving others - the FDA, a CRO - to review guidelines or plans to handle clinical trials - can help the firm access skills beyond its internal knowledge base. As such, execution uncertainty can be reduced.

Involving others, however, is not a panacea. More involvement without limits is not always better, and involvement does carry some risks. For example, a partner brings credibility and is thought to reduce financial uncertainty. However, depending on the partner, its intentions, skills, and goals, a partner can have a negative impact on the firm’s financial position, its ability to execute, and the competitiveness of its product. “One partner may reduce both financial and execution risk due to the deal terms, the partner’s experience and reputation, whereas another partner might not totally reduce financial, execution or product risk when the deal includes less funding, the partner has less experience with clinical trials or the product than anticipated.”

Learning

A by product of involving others, gathering and giving information can be that the firm gains new knowledge. When managers put this information to use they create new knowledge and learn. In the evolution of a biotechnology firm, learning is a critical way for firms to manage and reduce uncertainty. Learning works to reduce uncertainty because the knowledge gained can be used to act in different ways. In short, learning provides the firm with more tools to use in order to manage future unknowns. As one individual stated, “Whenever you don’t know, learn more!” “When you fail, ask why? What went wrong?” A culture of learning helps to establish an area of expertise which fundamentally reduces uncertainty - at least in that domain.

Learning is also important when there is an unexpected turn or failure. Like a silver lining, when examined closely a failure provides more information and better insight for firms that operate under conditions of uncertainty. To the extent that a firm uses this information to learn, it can help to reduce uncertainty by answering questions.

Learning can also reduce uncertainty by providing a direction. When surprises occur, managers can ask “What might we have done differently? If we change a protocol would that make a difference? Can we use what we have in our hands? What can we get, how quickly can we get there and what’s the probability that it’ll make it? Once we examine the situation, we have more information, so it should be more likely that we’ll succeed if there’s enough data to move forward.” When failure doesn’t point the firm in a specific direction it can at least help firms choose actions to bypass, circumvent, or make uncertainty irrelevant. “If an adverse event does not produce a convincing direction, then you can use what you know to figure out a way to deal with it, or go around it.”

Conclusions

For a small firm starting the long development path that is typical of biotechnology, uncertainty abounds. As the firm evolves uncertainty becomes more defined and readily attributed to financial needs, the firm's ability to execute, and issues related to the product. Later in the firm's evolution, each of these sources takes on additional specification.

These sources of uncertainty, while unique, are highly inter-connected. The uncertainties related to where the firm raises financial capital can affect whether the firm gains execution expertise, thereby reducing execution uncertainty. The source of capital can also influence product design choices and product uncertainty in both positive and negative ways.

Although uncertainty is ever-present, managers can reduce uncertainty through effective countermeasures that include planning, prioritizing, pacing, conserving, communicating, involving and learning. While each of these has been discussed individually, like the sources of uncertainty, the actions to manage uncertainty are clearly interlinked.

Planning key steps in the development process is guided by the priorities of the firm. Priorities might be adjusted as the result of communication that involves many individuals. Priorities can also change based on lessons learned and the desire to both conserve resources and maintain a strong pace of development.

The interviews with managers present some interesting insights and restate advice that, for some, is obvious. For example, raising funds and using them wisely is necessary, well understood advice. However, because of the intricate relationship among the sources of uncertainty and the actions that firms can take to manage them, many firms unwittingly overlook the ramifications of their actions:

Managers do choose not to raise funds, ignoring a pacing that the firm's environment presents. Instead, they focus on execution or design, confident that success in these areas will produce capital when the time comes. As one individual explained, "We weren't going to raise money. In fact, we had told everyone that we were going to wait until after the trials. Raising money wasn't part of the message. But a Board member brought up the idea that we might raise money. It was counter to our message, not something we had discussed. We did. And now we're able to move forward."

We also find support for the advice to include individuals from all areas – manufacturing, clinical quality, and marketing – early in the product development process. While not new to many managers, other decisions to deal with uncertainties such as maintaining a pace of work needed to quickly develop a product can inhibit the implementation of this practice. Instead, managers ignore the need to include others that aren't central to the issues at hand. "Marketing wasn't involved early on. We thought we knew the market and knew there would be support for our pricing strategy. Years later, the market has changed. We've had to rework the product market positioning and adjust manufacturing to be viable in the market. We might have made better choices with more involvement in the early stages."

The interviews also reveal insights that are somewhat counter-intuitive. For example, while managers may argue the benefits of a second product, we find that diversification is not a wise choice. Despite the arguments to the contrary "off the table ideas can grow arms and legs. Managers become attached and, wait to pull the plug until two times the budgeted funds are spent." Work on a second product can be "a huge distraction and a drain on funds." To limit the downside of second product development, firms can plan – identifying a point when efforts are to be discontinued.

The action of prioritizing also offers an interesting insight for managers. Despite the interconnectedness of the sources of uncertainty, individuals do not need to work on all uncertainties at one time. Instead, it is effective to have individuals manage only the uncertainties they face on a regular basis. By pooling these different activities, the firm is able to address many aspects of uncertainty in an efficient manner.

We also find that pacing that gets a product to market quickly, offers real and understandable benefits. However, in contrast to the idea that parallel processing will get the firm ahead, we find that a more measured pace can help the firm to avoid set-backs and consistently move forward.

Another critical insight is the need to include and listen to all aspects of communication including opinions and “gut instincts”. While these elements of conversation are often cautionary and viewed as “negative, alarmist, and counter-productive”, it is possible that these can be the nuggets that help the firm make critical changes in product design, momentum, and how capital is spent.

The evolution of a biotechnology firm from a small start-up to an established firm is a long and risky journey. Managing uncertainty that stems from financial, product and execution sources is a constant challenge that not every biotechnology firm overcomes. However, this need not be the case. Despite the ubiquitous nature of uncertainty, managers can take several actions that help to reduce, avoid or make uncertainties irrelevant. The keys to reducing uncertainty are to plan, prioritize, set a pace, conserve resources, communicate well, involve others and learn along the way.

estimates of drug development costs”, *Journal of Health Economics*. Amsterdam: Mar 2003. Vol. 22, Iss. 2; p. 151

ⁱ Where-ever possible, direct quotes from the interviewees are presented in quotation marks. To retain anonymity, the names of the individuals and the companies they represent, are not identified.

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