

Strategy from Science: Evidence-based scientific management principles for Pharmaceutical and Biopharmaceutical R&D Strategists

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Strategy as a Concept

Even if not explicit in a written or verbal plan, strategy is created, implemented and changed continuously in any pharmaceutical research and development (R&D) organization. The people charged with strategic responsibilities in pharmaceutical R&D organizations have widely variable training, industry experience, areas of expertise and personalities. In short, there is no archetypal pharmaceutical R&D strategist. Furthermore, the processes of R&D form a complex, dynamic system with many and varied inputs and people/process interconnectedness. For these reasons, methods for creating sound strategies—meaning strategies that more often than not result in actions that lead to desirable outcomes—should be universally understood and applicable in a wide variety of circumstances.

Viewed in this way, the concept of strategy as I will refer to it here is different from related activities such as “brainstorming” or short-term plans made in response to immediate needs. Rather, it is a conscious, ideally logic- and reason-driven, long-range planning process that serves a foundational role for related planning activities. It differs from policy only semantically in that policy is generally used to mean the default implementation of a strategy (or related group of strategies) across projects.

Although the type of strategic planning I’ll discuss here pertains solely to pharma/biotech (hereafter simply Pharma) innovation priority and process planning, the principles of scientific, evidence-based strategy are readily applicable to other corporate activities, such as financial and general organizational planning.

Pharma Innovation

Pharma’s growth has been driven by [technological innovations](#). That is, Pharma has grown primarily by improving old products or by creating new products and the processes that lead to new products. Compare this approach to innovation with, for example, the innovations made by Dell, which grew primarily by [business-model innovations](#). Dell, became an industry-leader in sales of PCs by improving its manufacturing, supply chain, and distribution efficiencies and then passing along these cost savings to consumers, who purchased products directly from Dell over the phone and internet. In contrast to the retail PC-business of Dell, business-model innovations have played a relatively small role in the overall growth of Pharma up to now. The basic business model of pharma has been questioned, and some innovations are being tested, such as direct distribution. This discussion, however, will focus on technological innovations.

The 1990's saw the rapid growth of Pharma, in terms of volume of product sold, value of product sold and firm valuations. This growth was fueled by many new product introductions. Creative and robust marketing disseminated these many new products into both older markets (e.g. statins and AII receptor blockers), growing them to record sizes and market value, and new markets (e.g. SSRI/SNRI and PDE V inhibitors), with equally dramatic results.

What was the impetus for this explosive growth in new products and product sales? We know that the drugs approved in the 1990's were discovered in the 1980's (and sometimes earlier). A confluence of advances in medicinal, formulation and process chemistries, coupled with rapidly expanding understanding of the molecular underpinnings of human physiology and pathophysiology allowed (for the first time) the rational selection of drug targets. These targets were chosen based on two major considerations: (1) They were believed by chemists to be susceptible to low-throughput screening of relatively non-diversified small-molecule libraries. (2) They were potential precursors to therapies that addressed large, unmet medical needs. Development (i.e. process) innovation strategies evolved to accommodate the filling of R&D pipelines by new molecules, but for the most part, these were incremental innovations that were ineffective in reducing the time or cost needed to develop new drugs. Indeed, as the decade of the '90's progressed, drug pipeline attrition rates remained the same or increased and [drug-development costs soared](#).

While rational target selection was initially very effective in finding new drugs, eventually the discovery of so-called "druggable" targets failed to keep pace with the demand for newer drugs to replace the chemical- or pharmacological-class pioneers initially discovered in the 1980's. The low-hanging fruit had been picked. The higher fruit that remained proved difficult to reach despite remarkable advances in our knowledge of the human genome and proteome during the 1990's as well as the advent of techniques such as high-throughput screening, computer-aided drug design, etc. aimed at improving the ability to find and create new drugs. Drug R&D spending continued to escalate exponentially, largely due to increases in clinical budgets, but the output of new-molecular entities fell. By 2001, as the wellspring of new drugs from the 1980's discoveries slowed to a trickle, we began to read of a "crisis" in R&D productivity.

In the meantime, the biotech industry gloated publicly, believing that any "crisis" in Pharma was *their* problem, not ours. But things change...quickly, in this case. After enjoying its own growth explosion in the 1990's, big Bio is now facing its own looming productivity "crisis". As the easy protein-therapeutic targets have been picked off, today's blockbuster proteins are destined to become tomorrow's biosimilar proteins, and barely a month goes by without an outrageously expensive protein therapeutic angering a lawmaker somewhere. Big Bio is feeling the pressure too.

What happened in Pharma R&D in response to this perceived productivity/innovation crisis? A lot of introspection. Senior managers began to admit publicly that their focus on the latest genomics findings and high-throughput molecular screening during the early 1990's was not paying off to the extent they had hoped. Most senior R&D managers in

big Pharma lost their jobs, because failure in Pharma R&D was not tolerated¹. Those managers brought in to replace the old guard decided that the first best strategy was to find out what the most successful companies in other R&D-intensive industries were doing to keep innovation growing. The underlying management strategy of driving growth through technological, [sustaining innovations](#) did not change. What changed was an almost frenzied race to implement the latest thinking in R&D innovation, gladly supplied by the major management consulting firms.

Strategic Management Today

As management consultants are wont to do, they recommended and oversaw implementation of a host of strategic and operational changes designed to ease Pharma's productivity pain. Here are a few: Performance Management Systems (e.g. Total Quality Management, Balanced Scorecards), Innovation Management (e.g. internal ventures, external ventures, innovation networks, innovation engines, centers of excellence), Quantitative Portfolio Management, including risk management and real options, Cultural Management (e.g. leadership culture, empowerment culture, entrepreneurial culture), Organizational Management (e.g. Heavyweight teams, Lightweight teams)...you get the idea. Many things were being tried, sometimes many things simultaneously in a single organization. The problem was not that Pharma tried (and continues to try) many different approaches to solve their perceived productivity crisis. The problem was that, almost uniformly, the approaches were tried **without sound evidence or clear rationales to support their implementation.**

Following implementation of changes to strategy or tactics, results were sought quickly to determine if changes were having their desired effects. They weren't the measures that signaled the crisis to begin with, like return on R&D investment or even gross output of new products into the market. Those measures would take years before decision-makers could react to them. So, instead, surrogate measures of R&D productivity were created—metrics that were believed, but not proven, to predict improved R&D return-on-investment. The amount of evidence supporting such beliefs was, in most cases, minimal.

The above scenario remains the norm today. Consultants and the managers they serve tout their transformational methods and results without the rigorous

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evidence scientists have come to demand from their own work. As an example of the types of changes made and metrics used, I've selected the case of Wyeth's R&D relationship with Accenture. Please do not think I have an axe to grind with Wyeth. I've chosen this relationship simply because Wyeth/Accenture have publicized their recent R&D re-organization and strategy development efforts in the [popular press](#) and on the [web](#).

¹ Failure is supposedly welcomed now, as long as one "fails fast", but actions speak louder than words and senior-managements' incentives are still geared towards fast success not fast failure.

Accenture calls their Wyeth R&D assignment “Workforce Transformation”. Accenture reportedly “transformed” Wyeth’s R&D workforce by “implementing a team-based structure” and a “governance structure that focuses senior managers on a single set of principles and improves senior management accountability.” Accenture and Wyeth “defined performance metrics for both individual R&D employees and groups [and] put it all together in a comprehensive balanced scorecard....” And the results? Accenture’s suggested changes were reportedly implemented **within just two months** [my emphasis], and within just three months of implementation “contributed to a 300 percent increase in the output of Wyeth R&D’s Drug Discovery operation.” Importantly, the “productivity gains”—which “have not negatively impacted quality”—“are sustainable over the long term.”

The above conclusions are fine for purposes of marketing Accenture’s consulting business. But it is important for strategists to distinguish between metrics suitable for promotion and those suitable for strategy refinement. The above claims are an example of the former: short-term measures that imply but do not demonstrate improvement in the business. For instance, a 300% output of drug discovery, all else being equal, might be a desirable outcome, but we are not told what increase in input (cost) was required to achieve this increased output. More importantly, the claim contains no evidence of the quality (i.e. present value) of the increased output. If previously low-value Discovery outputs were now being pushed forward, the effect would ultimately be decreased productivity as the NMEs made their way through the pipeline.

The Challenge of Using Evidence to Support Innovation-Management Strategy

The types of management studies that support implementation of the tactics discussed above are generally observational. The best of them summarize historical data on a handful of industries, representing perhaps a dozen companies and a few hundred products. Most, though, focus on just one or two companies and a handful of products. From these limited observations, statistical methods, such as regression models, are used to derive correlations between observed behaviors and outcomes. In some studies, these correlations are extended to cause-effect relationships by examining the temporal sequence of events, but more often than not, inferences of cause-effect are made with limited or no supporting evidence.

If pharmaceutical R&D managers have learned anything new about clinical science in the last few years, it’s that observational studies involving human actors (either individuals or organizations) under the best of circumstances are biased with respect to any given

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outcome in uncontrollable and oftentimes unpredictable ways and, when considered individually, are incapable of reliably associating cause and effect. Observational studies of business practices, which are subject to similar biases, almost never represent the best of circumstances. Collectively, observational studies that point to the same correlated phenomena occurring with the same temporal sequence, can provide some assurance that the observed phenomena represent a cause and associated effect. Theories explaining these relationships can then be created. If they stand the test of time, they will generally become accepted. This prototypical sequence of rational decision-making as a driver of strategic management practice is an exceptional one today.

Understanding these limitations, why do R&D managers—usually scientists who have been trained to be skeptical of unsubstantiated theories—so readily acquiesce to the unsubstantiated advice of management consultants? Is it because they sense the wisdom of these consultants, despite their failings to provide compelling evidence that support it? No way. Scientist-managers generally eschew wisdom unless it comes from other scientists, and even then accept it reluctantly. I think R&D managers react to unsubstantiated management advice for three reasons: (1) because that is what they have been trained by example to do, (2) because it is what they think they must do in order not to become scapegoats for the failures of their organizations to flourish subsequent to change and (3) because they think that heuristics (i.e. mental short-cuts and rules of thumb) that provide for sound decisions in the near-absence of strong evidence will suffice in these circumstances². I contend that each of these three reasons represents an abrogation of responsible leadership.

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On the other hand, what if R&D innovation managers are appropriately skeptical about management advice? What if they are so skeptical that, not seeing any better way, they have become cynical and now accept that R&D strategy and process management is, by its very nature, unscientific, impenetrably complex,

perhaps largely random, and therefore forever prone to the whims of management gurus and the pressured executives they cultivate. If this is the case, then studies influencing the practice of R&D management cannot be expected to adhere to the same scientific standards as inherently scientific pursuits, such as drug discovery, and why should they? What's the use? To a manager that espouses this view I would offer this advice: Quit your job now, because you serve no useful purpose to the organization, other than as an impediment to its progress. If there is no hope for rational thought based on empirical evidence to drive strategic decisions in Pharma R&D, then there is simply no hope.

Whether innovation strategists feel compelled to accept unsubstantiated strategic advice out of habit or fear, or whether they are lulled into it because of cynicism bordering on

² See, for example, a discussion by Gerd Gigerenzer on “smart heuristics” at http://www.edge.org/3rd_culture/gigerenzer03/gigerenzer_print.html

fatalism, the situation must change if innovation strategy is to become more rational and less emotional...more skillful and less chancy...more orderly and less chaotic.

Applications of the Scientific Method in Management Strategy Development

All scientific theories are fundamentally judged on their soundness by their adherence to at least three major principles:

- testability (i.e. a scientific theory must be subject to being disproved),
- predictability (i.e. a scientific theory must be repeatable and capable of being predictive),
- interpretability (i.e. a scientific theory must be explanatory and capable of determining cause and effect relationships)

These principles are therefore underpinnings of the [scientific method](#)—the collection of principles and practices used to generate and test hypotheses and develop them into theories. The scientific method seeks to describe the objective truth of a phenomenon. It relies on empirical (i.e. observable) evidence to support this truth.

The scientific method seeks to describe the objective truth of a phenomenon with empirical evidence.

Must an experimental approach be taken prior to every major tactical or strategic decision? No, of course not. The types of controlled, bias-limiting, hypothesis-testing experiments routinely used in the natural sciences are nearly always impractical or impossible in the management sciences. Managers must rely on the powers of observation, deductive reasoning and [inductive generalization](#) to form strategy. Implicit in this process is the creation of [mental models](#).

Mental models—representations of perceived reality—are used ubiquitously by Pharma R&D managers. Such models are believed to be the primary tool used to create strategy from limited empirical evidence. The same tool is used to create tactics from strategy and to implement tactics by selling the strategy to the organization. In some cases, mental models alone can yield effective results. But mental models have profound limitations that make their use as the sole tool by which to forge strategy in the complex environment of Pharma R&D folly. [Doyle et al](#) have summarized these limitations:

- People model explicitly what they perceive is true but not what they perceive is false;
- People typically rely on the simplest model to represent reality, because working memory limitations make it impossible to simulate complex dynamics;

- Causal pathways of mental models often have gaps or omissions and sometimes lead to dead ends, relationships between variables are often ambiguous, and variables are rarely described quantitatively;
- Mental models are prone to errors and biases that result from biased information processing, unwarranted assumptions, overconfidence in one's knowledge base, and other barriers to learning;
- The parts of a mental model that are brought to bear on a particular decision or problem depend on what external and internal cues are present at that particular time to “jog” one's memory, leading to model instability;
- Mental models typically fail to account for important time delays that can create instabilities in systems;
- People have particular difficulty perceiving and representing relationships between variables or time series data that are nonlinear. Such relationships are almost always simplified and represented mentally in a linear fashion;
- Mental models often fail to incorporate important feedback mechanisms, substituting unidirectional cause-effect relationships;
- Causation in mental models is over-simplified, tends to amplify the importance of events close in time and space, and ignores the structure of the system itself as a source of causation;
- There are significant delays when updating mental models with new information.

Putting Evidence and Mental Models to Work Together with Computer-Aided Systems Modeling

When empirical testing under “scientific conditions” is impractical, as it usually is in business, simulated functioning of the business using mathematical models can inform strategy by providing evidence to revise mental models. Simulations that provide for dynamic changes to the business over time will be more relevant than those requiring static conditions. One simulation technique that has been deemed useful in a variety of complex business situations is [System Dynamics](#) (SD).

Organizations and their processes that result in innovations comprise open, [complex systems](#)—networks of inter-related and inter-dependent actors that are influenced by and respond to internal and external cues. SD models are [deterministic](#). This means that for any given current state of the system, a future state may be [predicted](#). Note that the predictability of a future state of a system will depend on how much is known about its current state. In other words, imperfect knowledge of the current state leads to imperfect prediction of a future state. Therefore, the quality of evidence used to create an SD model will greatly influence the quality of its predictions.

Recognizing the cognitive and biased-learning limitations of mental models for devising strategy (or policy) in open, complex systems, SD practitioners have harnessed the power of computers to assist in the iterative process of updating mental models with the goal of making them more accurate (and thus more predictive) and more dynamic. Computers address most of the key limitations of unassisted human mental modeling (again, these concepts are taken from [Doyle et al](#)):

- Computers allow people to create and simulate models of great complexity;
- The process of building a working computer model encourages operational thinking (i.e. thinking about phenomena as they actually, as opposed to theoretically, operate) as well as completeness, coherence, and quantification in formulating mental models;
- The computer simulation, in contrast to a mental simulation, is consistent and reliable;
- The computer's ability to store and retrieve information exceeds the capabilities of human long-term memory, which is subject to forgetting, retrieval failure, and distortion;
- The virtual system is not subject to time limitations. Hundreds or thousands of simulations can be run in the virtual system in the time it would take to cycle through the real system just once;
- The virtual system allows for the type of systematic, scientific experimentation that is rarely possible with real systems. Variables can be changed one at a time to observe their effects in isolation. Actions that would be avoided in the real system due to irreversible consequences can be taken without fear in the virtual system;
- Virtual feedback is complete, unambiguous, and always perceptible;
- In the virtual system, there are no barriers to action and decision rules are implemented perfectly;
- The structure of the virtual system is completely open and available for inspection.

Let us examine, by way of theoretical example, how a mental model might be formed in Pharma R&D, how it might be used to create a strategy, and how modeling with the assistance of a computer (i.e. a virtual system) might impact the scenario.

I recently published a [Perspective](#) article for *NRDD* that describes the seemingly universal Pharma practice of racing to develop novel drugs quickly, with little or no consideration for the impact of market entry order (beyond striving to be first). This article was a review of theoretical and empirical management literature on the impact of market entry order on eventual commercial success coupled to a small, hypothesis-generating observational study of relatively recent pharmaceutical sales. In other words,

the article was intended to provide food for thought on the relationship between market entry order and eventual commercial success of drugs. It was not intended, nor should it be construed as, definitive evidence of predictable cause-effect relationship that can be translated into recommendations for action.

The above caveats notwithstanding, let's suppose that a consultant offered the following advice after reading the article:

Under conditions of an inherently flawed drug-class pioneer (based on knowledge gleaned from competitive intelligence activities) and untapped, potentially large markets (based on knowledge from primary and secondary market research), it is advisable to take a watch-and-wait approach before racing to compete with the class pioneer for first or early-entrant market status.

Would this advice be valuable? Certainly, the advice might reflect the objective “truth” of the matter. The data shown in the article certainly cannot be used alone to refute the above inference. In fact, the evidence already collected might be sufficient to make this conclusion valid. Or it might not be. The problem is that there is no way to know—under typical Pharma R&D management practices—without implementing the change, perhaps as a pilot program, and comparing the outcome to historical or concomitant control strategy to see “if it works.” Of course, if it works in one or even two cases, which is a large number of observations for new drug launches and requisite follow-up to ascertain commercial success, is that then a definitive finding? How will all of the other factors that might have influenced the commercial success of one drug program relative to another be identified and controlled? What if other firms react to the pilot strategy and change their development strategies in reaction? Is the newly implemented strategy still the correct one to pursue more broadly under these new circumstances? Get the picture? If not, the point is that pilot programs with prospective evidence collection are not any more conclusive than observational studies, and as we see with this example, they are not necessarily practical either.

Most of the key strategy decisions taken by R&D management are of the type above. That is: Relatively small changes to an investment decision can have potentially large financial implications (i.e. the relationship between cause and effect is nonlinear); there is a long time interval between cause (implementation of strategy) and effect (sales or profits); and many factors operating simultaneously influence the outcome in complex ways, but the strategy focuses on one or two factors in relative isolation from all others.

Imagine that, instead of relying solely on a simple mental model created from scanty evidence, the above market entry order strategy is developed using a large amount of cross-sectional data (i.e. data captured at about the same point in time) relating sales to market entry order and to other factors, plus a smaller set of longitudinal data (i.e. data comprising a [time series](#)) containing similar information that, together, are used to calibrate a model that predicts the outcome of sales based on a variety of internal and external factors for a given product. In this case, many factors may be adjusted

simultaneously to examine the combined effects of factors on the outcome of interest. Perhaps with this approach a model will suggest that entry order will be more important when commercial spend is factored. Perhaps for a fast-second the time prior to the third in class will mean more to lifetime sales than the time delayed relative to the first in class. Perhaps the primary endpoint chosen for the pivotal clinical trials will have the greatest effect on NPV if it influences the proportion of sales reimbursed by third-party payers by at least $x+5\%$ at launch, where x is the proportion of sales reimbursed by the pioneer at the time of the follow-on launch, regardless of whether the drug is first or third in class? As I am purposely demonstrating with this example, the quality of learning that can occur using a computer, skillful modeling and objective evidence is profound. The impact this learning can potentially make if translated into sound strategy and actions is equally profound.

Next Steps

It is not yet time for conclusions. There is much more that must be said, and even more importantly, must be shown, before concluding anything that could be accepted and used to change practice. This I know too well. But I consider this a good point to stop for now. I encourage readers who are managers in Pharma to isolate a couple examples of innovation strategies made and implemented at your company recently. Ask yourself about the evidence used to derive the strategy. Was it sufficient to determine cause-effect relationships? Was it comprehensive in scope? Also, see if you can infer a mental model that might have been used to derive the strategy from the available evidence. Make note of the model's limitations by developing a list of some obvious factors it must have omitted; imagine how those factors might have related to one another and you will begin to see firsthand the power of computer-aided modeling and evidence-based scientific strategy-making.