

# PAYBACK: MAKING INNOVATION COUNT IN UNCERTAIN TIMES

*Drug companies need to foster innovations based on their ability to generate cash returns.*

BY PETE LAWYER, JAMES P. ANDREW, PETER TOLLMAN, PHD  
AND MARTIN B. SILVERSTEIN, MD

- The pharmaceutical cash flow equation has changed radically and pharmaceutical innovation is not generating the same financial payback that it once did.
- Pharma Executives should re-think innovations based on their ability to help companies navigate the four key elements (S-Factors) of the cash curve: start-up costs, speed to market, support costs, and scale operations.
- Some innovations will negotiate the gauntlet of the four S-Factors and generate payback; others with apparently equal potential will get hung up in the cash curve and never generate a positive return.

The world is full of brilliant ideas and the pharmaceutical industry has seen its fair share. With gross margins in the 90% range and long, patent-protected revenue streams, it doesn't take a lot of hits to earn a decent payback on the initial investment. But the fortunes of the pharma industry have turned and the old payback equation no longer works. Good science that does not result in a cash flow stream is more than just an unfulfilled promise – it is a significant drain on the entire organization and a potential black hole for shareholders.

A recent *BCC/BusinessWeek* poll of 1,070 senior executives ranked Apple, Google, 3M, Toyota, and Microsoft in the top five slots. How did the pharmaceutical sector fare? Quite poorly, according to respondents: only

**Genentech Inc.** (27<sup>th</sup>), **Pfizer Inc.** (55<sup>th</sup>), and **Amgen Inc.** (87<sup>th</sup>) break into the top 100. To be sure, the survey wasn't answering the questions about breakthrough science at leading life sciences companies. Rather, the poll asked about the nature and process of innovation itself—and which companies exemplified these traits by virtue of the products and services they bring to market. These qualities and the inside stories from some of the world's best innovators are the subject of a new book called *Payback: Reaping the Rewards of Innovation* by two partners at The Boston Consulting Group, Jim Andrew and Hal Sirkin (Harvard Business School Press, 2007). The lessons for the pharmaceutical business are compelling.

After all, it is no secret that the process of

pharmaceutical innovation is in serious need of an overhaul. The number of new molecular entities (NMEs) approved by the Food and Drug Administration has fallen steadily, from 142 in the 1994 to 1997 period, to 116 in 1998 to 2001, and 87 in 2002 to 2005. Meanwhile, the probability of success for compounds in the preclinical stage has tumbled to about 10%—well off the pace of 10 years ago. Combined with increased scrutiny on product approvals, intense focus on safety and clinical evidence, and great uncertainty over future pricing in the world's largest and most lucrative markets, pharmaceutical executives need to rethink the approach to innovation in their business with an eye toward cash flow. Not only is this a major turn of events in a sector that has always been able to bank on the future, it represents a monumental challenge because the time horizon for cash flow management extends 20 years into a cloudy future.

## THE PRIMACY OF CASH

At the heart of the payback concept is an immutable law of business: that all innovations need to generate returns over a reasonable period of time to fund ongoing operations, fuel future growth, and compensate shareholders for putting their capital at risk.

Companies place a series of bets, or projects, to bring new ideas to market, and each project has a distinct economic profile. It is called the “cash curve” and it has several components, as illustrated in Exhibit 1:

- *Idea generation*, extending from the very first idea to proof-of-concept

- *Commercialization*, beginning with commitment to launch and typically involving some form of process scale-up and commercial investment

- *Realization*, covering the innovation’s productive life cycle, or payback time, during which cumulative cash flow should cross over into the positive and shareholders get their just rewards

Successful payback rests on how the innovation performs on the four “S-Factors” outlined below.

*S1. Start-up costs* determine how large a financial down payment the innovation entails. The deeper the downstroke, the more positive future cash flow is required to keep investors whole.

*S2. Speed-to-market* dictates how quickly companies begin to register sales for their new ideas. The greater the speed, the faster the returns, and the better the market position.

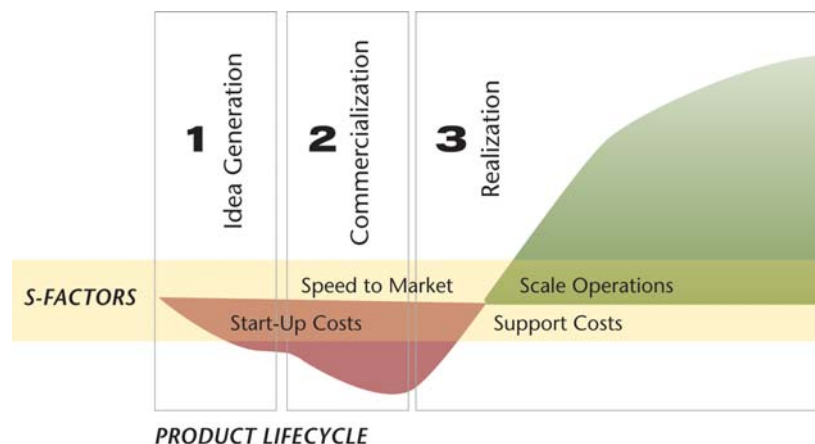
*S3. Support costs* include COGS, sales & marketing support, G&A and any ongoing R&D requirements. All of these factors represent expenses that constrain the amount of free cash flows generated by the innovation.

*S4. Scale operations* imply that the idea has passed the initial build phase, cash flows have reached equilibrium and – with luck and good planning – the capital and infrastructure requirements to bring the idea to market are now being amortized successfully.

Some innovations will deftly negotiate the gauntlet of the four S-Factors and generate acceptable or even spectacular

Exhibit 1

## The Cash Curve



SOURCE: Payback: Reaping the Rewards of Innovation

payback to their backers. Other innovations, with apparently equal potential, seem to dawdle endlessly in the commercialization phase or fail to reach scale operations, consuming cash while tantalizing management with the promise of future payback.

### THE PHARMACEUTICAL CASH CURVE

The details and structure of the cash curve will clearly resonate with pharmaceutical executives. After all, the business is organized around distinct activities (discovery, development, commercial) that map closely onto the three cash-curve phases as outlined above. But the shape of the curve has changed over the past ten years – dramatically affecting payback.

Using data from a BCG study on productivity and product approvals, we made five input assumptions for hypothetical product launches in 2006 versus 1996.

- Average discovery cost per candidate (a lead development candidate entering pre-clinical testing) falls from \$70 million to \$50 million, thanks to improvements in target identification and validation as well as adoption of new technology. Our assumption may be optimistic: a recent *IN VIVO* article cited the total risk-and-time adjusted cost of a pre-clinical candidate at \$78.3 million. (See “The \$100 Million IND,” *IN VIVO*, November 2006.)

- Development cost per candidate rises

- by 30% owing to higher cost per patient

- Probability of launch declines from 18% to 10% due to a higher proportion of novel targets, higher hurdles for safety and efficacy, and more stringent target product profiles

- Time to peak sales improves from 10 years to 6 years as companies reduce clinical develop-

- ment time and speed up global product roll-out

- Net margin per compound falls from 50% to 40% due to increased price pressure

Given these changes, the cumulative net cash flow required to reach top quartile returns climbs to around \$7 billion. Taking into account the initial cash outflow and the time value of money, average peak-year sales would have to reach nearly \$1.7 billion to achieve a 15% return on investment. (See *Exhibit 2*.) In other words, the pharmaceutical sector would be even more hostage to blockbuster compounds than in the past – at a time when the world’s payers are less likely to confer such an honor on new medications. If average peak sales for a company muster, say, a still-impressive \$1 billion in annual peak sales, pharmaceutical returns would tumble to around 10% under the assumptions above. At this point, most investors would flock to the relative safety and reliability of an S&P Index fund.

This example is not meant to indicate all pharma companies will regress to a common low point. In fact, the more likely outcome involves winners and losers, with those leading the charge setting new standards for efficiency and cost-competitiveness. To get there, however, the new leaders will need to make better decisions that lower the cost of failure and success. This involves a substantial departure from traditional recipes for R&D and commercial success and an intense focus on ways to cut

the start-up and support costs, increase the speed to market, and maximize the efficiency of scaling operations. To examine how this might work, it is useful to review pharmaceutical company activities and behavior using the four S-factors.

### START-UP (S1): BRUTE FORCE IS OVERRATED

Anyone who has spent time in a pharmaceutical company knows that there are distinct cultures in evidence across the organization. Discovery research tends to be dominated by scientists attempting to ferret out faint signals from complex biochemical reactions. For them, time to market is less of an imperative. Valuing their work is notoriously difficult because the units of activity—targets and mechanisms of action—are quite difficult to assess at this stage of the game. Frequently, the only measurement that carries weight is the absolute number of compounds that make it to the clinic—a decidedly flawed measure of value.

But the difficulty of measuring the process doesn't mean it shouldn't be done. Instead, companies need to dispassionately review discovery phase inputs and outputs to gauge how they should approach the start-up phase. Precise numbers for discovery research can be difficult to obtain, but total R&D cost per company is readily available. Assuming a 20% to 25% allocation of the R&D budget to discovery, the industry's top 10 companies can be expected to plow a whopping \$500 million to \$1 billion apiece into discovery research. Going back to the pharmaceutical cash curve example above, a 10% yield on internally generated compounds implies that the majority of this investment won't repay the effort.

Is the problem the intractable nature of discovery itself? After all, it is a very uncertain business to chase

molecules looking for a reaction against targets that may or may not in turn have an impact on a particular disease. From a capital markets standpoint, early-stage biotech shares encapsulate the huge upside from a positive outcome along with the much more likely scenario of failure. Investors, including large pharmaceutical companies, can place discrete bets on individual technologies or conclaves of scientists they feel have a competitive edge. Conversely, such bets are averaged across the entire pipeline and current earnings of a large pharma company—which reduces exposure to be sure—but also obscures visibility.

In part for this reason, **GlaxoSmithKline PLC** adopted its Centers for Excellence in Discovery and Development (CEDD) model, which permits focused risk-taking and greater transparency of results. Although GSK's approach has yet to achieve full vindication, there are early signs that it might be paying off. In the 5 years since the model has been up and running, the CEDD have doubled GSK's pipeline to an industry leading 45 NCEs in Phase II and 11 NCEs in Phase III development. With market success still uncertain, GSK has injected further vitality into

the equation with the introduction of an additional center—the Center for Excellence in External Discovery and Development (CEEDD)—which competes with the CEDD and is charged with scouring the external market to identify promising compounds. As of June 2006, GSK has 48 programs in its current CEEDD portfolio. (See also "GSK's Risk-Sharing Deals to Compete with In-House R&D," *IN VIVO*, March 2006.) Other companies have chosen to retain the organizational model but shift accountability for discovery leadership further downstream to include POC (proof-of-concept), thus rewarding not only the quantity of candidates, but their probability of success as well.

Since the future is so distant and so inscrutable from a discovery vantage point, looking to the outside could well be the best way to address the crucial issue of start-up costs. Beyond the models referenced above, other organizations are tapping into the rich scientific tradition of universities to spur discovery research. (See sidebar: "Time-Based Discovery: The Myelin Repair Foundation.") Alliances with new players such as this would enable Big Pharma to pool risk and spread its bets to

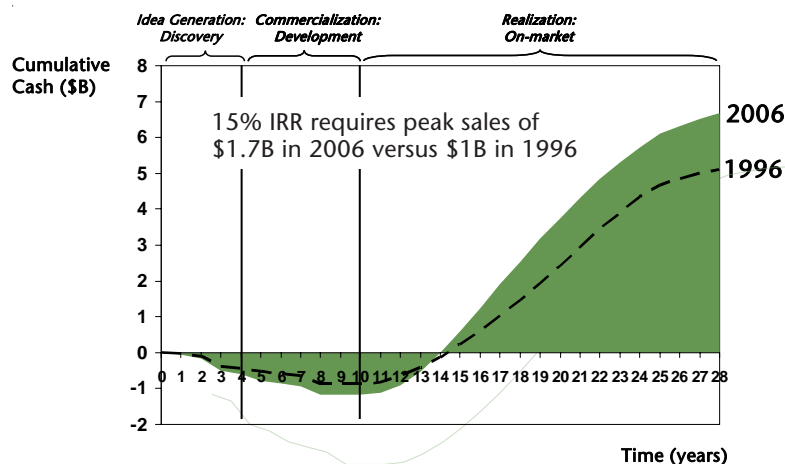
counter the challenge of the ever-deepening financial downstroke and uncertain payback for discovery research.

### SPEED TO MARKET (S2): FASTER, BIGGER, SMARTER

Further downstream, activity and innovation move to the clinic, where physicians, statisticians, and other experts have made an art form out of structuring clinical trials designed to isolate and highlight specific aspects of patient response. Although time is of the essence at this stage, a poorly designed or badly executed trial can lock in years of under-performance or worse. The race to market typically involves a series of trade-offs in which clini-

Exhibit 2

### The Changing Pharmaceutical Cash Curve



- 2006 has overall 10% probability of success per GLP/Tox start versus 18% in 1996
- 2006 has 10% lower net margin and 30% more development costs per candidate versus 1996
- Time to peak sales is 6 years in 2006 versus 10 years in 1996.

SOURCE: The Boston Consulting Group analysis

cal development managers weigh the merits of gaining a little more insight about a molecule against the realities of a finite patent life and hard-charging competition.

The problem is that arguments over these trade-offs can muddy the key strategic imperative of the theory of payback: once past proof-of-concept, the need for speed is paramount. Nevertheless, many companies have a hard time shrugging off the reflexive desire for more proof. This is especially true for drugs targeting multiple indications, such as many oncology and immunology compounds, which compete for funding with medications for primary care or large specialty areas such as cardiology. It is tempting to await positive results from a trial in one indication before committing to fund others. However, simulation exercises typically indicate that parallel trials are the dominant solution.

This rule of thumb rests on two core

assumptions. First, the aggregate value of a multiple-indication compound may well eclipse that of single-indication drugs. For instance, Amgen's etanercept (*Enbrel*), **Abbott Laboratories Inc.**'s adalimumab (*Humira*), **Johnson & Johnson** division **Centocor**'s infliximab (*Remicade*), and other TNF-inhibitors together chase indications for Crohn's disease, rheumatoid arthritis, psoriasis, ankylosing spondylitis, and other chronic inflammatory ailments with aggregate annual US sales exceeding \$4 billion. If these products had to battle for position in a development portfolio on the strength of a single lead indication rather than overall compound value, they might well have slid down the queue.

Second, the method of action or underlying condition for multiple-indication compounds has to be related in a way that a trial for one provides substantial information about another. For cancer drugs—especially for solid tumors—there

is often some genetic component that links outcomes for one indication with likely results for other cancers. If the linkage is strong enough and the individual indications are worth chasing, the clearest and fastest route to the highest expected value involves parallel trials. Ultimately, the genetic linkage explains why **Roche** paid so much for **Plexxikon Inc.**'s BRAF mutation inhibitor—\$40 million up front for the IND stage compound, an estimated \$150 million in development milestones, and another \$500 million-plus in sales milestones along with royalties. The structural change that causes the particularly virulent cancer

addressed by the Plexxikon compound appears in more than 70% of melanomas—the drug's initial target—but it also shows up in many different solid tumors, albeit much less frequently.

True, parallel trials will require a larger up-front investment—at a time when the risk of failure has already risen to dizzying heights. If the financial exposure is too great for one company to shoulder, this risk can be managed through co-development arrangements or even out-licensing. When companies delay development of promising indications to await a further positive signal on an already good bet, competitive products wind up siphoning off market share for the entire life cycle of the product. That's why, for example, **Schering AG** (now a division of **Bayer AG**) teamed up with **AstraZeneca PLC** to share costs and responsibilities for Schering's early-stage anti-cancer selective estrogen receptor down-regulator. And more experimentally, it's why **PDL BioPharma Inc.** split the development of daclizumab (*Zenapax*) between two companies—Roche and **Biogen Idec Inc.** Roche ultimately backed out of the deal—but the fact that it was willing to let Biogen pursue the multiple sclerosis indication while it took on asthma and transplant rejection indicates that it takes seriously, and is willing to deal innovatively, with the costs, risks, and development-speed requirements of multi-indication products. (See *"Bigger Deal Values by Splitting Indications: PDL's Experience,"* IN VIVO, February 2006.)

Not all improvements require deeper scientific insight or higher-quality decision processes. Some of the barriers to innovation are simple human behaviors that are present wherever two or more people gather. Companies first need to get the innovation killers in check before they can get on with the breakthroughs that make payback possible. (See sidebar: *"The Innovation Killers."*)

One of the greatest ironies of the pharmaceutical R&D productivity decline is that advances in genetic understanding and disease markers should be making life easier. Biomarkers can help with both patient selection and follow-up, which in theory ought to limit the cost and extent of drug trials. The well-known case of trastuzumab (*Herceptin*), Genentech's \$1.2 billion drug for treating metastatic

## THE INNOVATION KILLERS

No matter how progressive a company may be, its business systems are generally designed for standardization, risk reduction, and clarity—in a word, control. The creative process, on the other hand, can look a lot like chaos: it forges connections that aren't obvious, often defies logic, and sometimes presents fully formed opportunities spontaneously. In an attempt to control the chaos, many companies unwittingly strangle creativity. Here is a list of common innovation killers stalking the halls in virtually every company:

- **Strategic Dissonance.** Poorly aligned strategy or operating metrics cause different parts of the organization to clash over innovation priorities and resources.
- **Unfunded Mandates.** The CEO wants the company to be more innovative ... but invests very little in innovation capability and capacity.
- **Token Gestures.** A small innovation group is formed to generate new ideas and propose new products, but the leader lacks sufficient authority or respect to garner funding or operating group support.
- **Quarterly Innovation.** By obsessing over quarterly numbers, management effectively rules out support of projects with a longer-term payback.
- **Dynasties.** Current or past franchises continue to consume the bulk of innovation resources, even when more attractive or tenable prospects beckon.

breast cancer, certainly bears this out. Today, physicians test breast tissue for the Her2 gene and those cancers that test Her2-positive are treated with *Herceptin*, thus maximizing beneficial response while minimizing toxicity.

But the real story begins upstream, where Genentech's Phase III trial randomized patients with Her2 over-expressing metastatic breast cancer to receive standard chemotherapy or chemotherapy plus *Herceptin*. The company points out that a standard trial would have required at least 2,200 patients and a 10-year period to achieve its end point. Pre-selecting patients with Her2 positive cancers meant that only 469 women were needed in the study to show a statistically significant survival benefit. Meanwhile, recruitment was completed in just 19 months. Further, Genentech gained insight about the disease pathways from *Herceptin* research, which in turn helped the firm design a next-generation experimental drug, *omnitarg*, now in Phase II trials. The benefits of this approach may not be a panacea, but lowering costs and shortening the time for development may be the only viable path to acceptable payback in a cost-constrained future.

### SUPPORT COSTS (\$3): RAGE AGAINST THE MACHINE

Arguably innovation is most sorely lacking in pharma's commercial activities. Share-of-voice marketing has been the time-honored tradition among competitors—as evidenced by the armies of drug detail reps massed on the doorsteps of potential prescribers. Although this leads to a margin-depleting sales and marketing arms race, no one—until recently—has wanted to be the first to withdraw the troops. After all, the marginal cost of pressing an incremental pill is next to nothing—so a small promotional response justifies high selling costs. But decades of pharmaceutical sales behavior has triggered an immune system response. Rather than viewing drug companies as natural allies in the war on disease, payers are more likely to lock horns with their medicine suppliers over price and access.

With margins looking increasingly vulnerable, many companies are thinking of ways to retool the machine. Pfizer's recent decision to lay off 2,000 reps, nearly

20% of its sales force, and cut \$440 million of annual expense, is perhaps a leading indicator that the arms race is finally drawing to a close. However, there is a limit to such maneuvers—ever more draconian cost-containment measures won't get the whole job done.

Meanwhile, unmet needs abound. Patient compliance with their drug therapies remains one of the most pervasive problems in the industry, reducing pharmaceutical efficacy and hurting sales to boot. Health economics and outcomes research are demanded, but they are often dismissed as biased when provided by drug suppliers. Direct-to-consumer approaches educate patients and drive sales, but often at the expense of harmonious relationships with doctors and payers, and potentially legislators and regulators. Drug companies that are able to build trust and transform the adversarial relationship with payers will likely find their efforts duly rewarded if they can in fact demonstrate better patient outcomes and a compelling clinical and financial value equation.

Still, progress is being made. Data-mining of electronic medical records

(EMR), for instance, enables real-time feedback from the clinic to the laboratory. **GE Healthcare**, a unit of **General Electric Co.**, helped study coordinators speed recruitment for a hyperlipidemia clinical trial by querying the investigation sites' records to identify eligible study candidates. Future EMR systems will enable pharmacovigilance and health outcomes by examining the "real-time, real-world" effects of a drug via an ongoing de facto "Phase V" trial. As such, data mining could help an antidepressant manufacturer demonstrate that its agent is correlated with weight loss, blood pressure reduction, or fewer hospitalizations, thereby helping the manufacturer differentiate it from competitors with similar primary antidepressant potency.

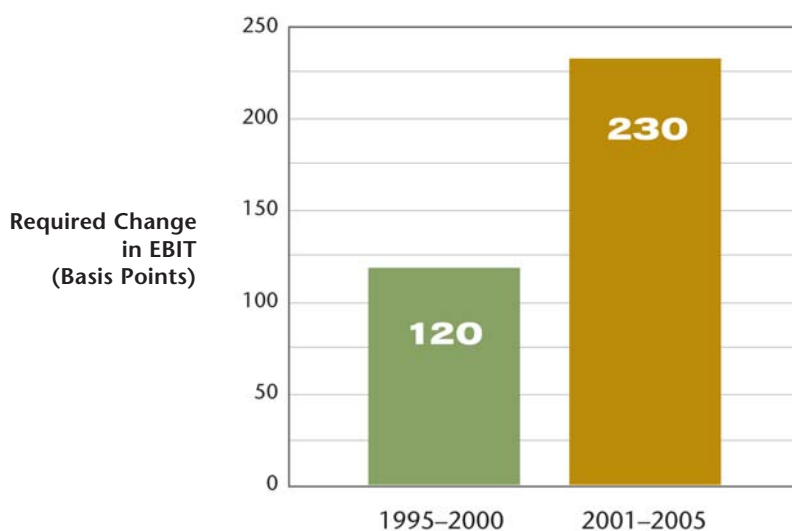
### SCALE OPERATIONS (\$4): SHOW ME THE MONEY!

Once a product has hit peak sales a portion of its cash flows are used for ongoing lifecycle management, but the remainder has to be enough to fund corporate overhead and future products. Past generations of investors have typically rewarded successful pharmaceutical companies with lofty

Exhibit 3

### Top Line: More Important than Ever

For an investor, what change in EBIT is equivalent to a 100 basis point change in sales growth?



SOURCE: Compustat; BCG ValueScience Center analysis

price-earnings (PE) ratios that signal great confidence in the underlying recipe for value creation.

But not anymore. PEs for the top 10 pharmaceutical companies have tumbled from a high of 39 in 2000 to 18 by December 2006. Investors have lost confidence in Big Pharma's ability to grow earnings.

Drilling a bit further on this point, it is

useful to remember that the PE ratio reflects expectations of future earnings growth, which can come from higher sales or increased margin. Today, investors are demanding evidence of top-line growth as insurance that the margin from current products won't be eroded by price pressures—or by continued poor R&D productivity.

BCG uses a market-based multiple re-

gression methodology to explain share prices and value creation for various market sectors, including pharmaceuticals. As recently as 2000, pharma investors would have been largely indifferent between top-line growth or increased EBIT. By 2005, with the future of pharma pricing harder to foretell, investors demanded over twice as much EBIT—or real cash in the till today—in exchange for the same amount of sales growth. (See Exhibit 3.)

What does this imply? At least at this point in history, it suggests that investors believe that the pharmaceutical market has become a cash-flow business, somewhat akin to consumer goods companies. After a period of retrenchment to ensure that operating costs are in line, pharmaceutical companies need to get back to the business of innovation and top-line growth. For this, they might borrow a page from the Apple playbook.

### APPLE: THE WORLD'S MOST INNOVATIVE COMPANY

To drive consistent innovation and ensure payback, companies need to maintain a complete picture of the cash curve so that ideation, commercialization, and realization remain in tune. Apple Corp.—voted most innovative company in the 2006 *BCG/BusinessWeek* poll—offers a case in point with its blockbuster success, the *iPod*.

Like so many good ideas, the *iPod* was really invented somewhere else. It is, after all, just a repackaged MP3 player. Through Apple's perseverance and self-belief, however, the *iPod* graduated to become the most successful consumer electronics product in history, eclipsing the previous superstar, the Sony *Walkman*.

Apple's *iPod* has all the hallmarks of pitch-perfect innovation management, including a deep understanding of the customer, a skillful blend of design and technology, and a corporate culture that propels ideas from innovation to cash. Against that background, Apple executives might have plotted a confident cash curve—but like all prudent managers, they were conservative. *Start-up costs* were remarkably low: an estimated \$10 million in development, with fewer than 50 people working on the project at any one time, and over a period of just eight months. As for *speed to market*, the company optimized that with an assortment of tactics. It used many off-the-shelf

## TIME-BASED DISCOVERY: THE MYELIN REPAIR FOUNDATION

The classic process of scientific discovery is a slow one, relying on academic research with peer-reviewed publication and rebuttal. When you have a progressive disease like multiple sclerosis (MS), this glacial cycle time is a source of serious frustration. So it was that Scott Johnson, a 50-year-old MS patient and former BCG manager began to look into the state of MS research. What he found was an under-funded, sluggish, serial process, with such poor information flow that important discoveries often took 3-6 years to reach print, and several more years before becoming applied science in a pharmaceutical lab.

For patients to benefit from breakthroughs in their own lifetimes, the pace needed drastic quickening. To that end, Johnson set up the Myelin Repair Foundation (MRF). Myelin is the fatty insulation that coats and protects nerve axons, which transmit electrical signals throughout the nervous system. In MS, the body's immune system attacks and breaks down the myelin sheath. The MRF identified, and then brought together, a "dream team" of five researchers from US and Canadian universities. MRF offered to raise \$25 million to underwrite research across their institutions, and any other contracted research that was necessary to get the job done within a five-year time period. To access the funding, the scientists had to agree to collaborate in real time—thereby avoiding publication delay—and to share patent rights and royalty revenues, which would be controlled by the MRF.

All five researchers contacted by Johnson accepted the proposition, at least in part because **National Institutes of Health** funding was increasingly difficult to secure. Halfway through the allotted period now, with just \$13 million allocated and \$5 million disbursed to the university labs, the MRF is posting exciting breakthroughs. They have filed nine patents, identified ten targets, and named nine drug candidates. Compared to average pharmaceutical industry performance of \$50-78 million per candidate and four years from initial experimentation to pre-clinical development, the MRF has shown a way to cut time in half while reducing cost by an order of magnitude.

MRF's early success is rooted in three clever notions. First, the time reduction occurs when leading scientists begin communicating regularly and building on each other's work, in the process unleashing a torrent of pent-up productivity. Second, the MRF benefits from leveraging the infrastructure at five world class laboratories, each one heavily subsidized by its respective academic institution. Third, and arguably most important, MRF taps the wisdom of Joy's Law, which stipulates that "No matter who you are, the smartest people in the world work somewhere else." The MRF has shown a way to tap their expertise in a collaborative model that just might lead to a cure for one of the world's most debilitating conditions.

components from suppliers and partners, for instance. And it deftly developed music industry relationships to create *iTunes*, its online music store, just as the industry completed electronic licensing agreements with their artists, thereby gaining a critical first-mover advantage and a substantial competitive barrier as users developed their own—legal—music libraries. *Support costs* were kept well in hand: the company presciently contracted Toshiba to supply the hard drives, and negotiated to buy its entire output for 18 months, thereby helping to obstruct competitor entry, control the price, and build a huge customer base for follow-on innovations such as the *Shuffle*, *Nano*, and *iPod Video*. *Scale operations*, accordingly, came extremely rapidly—almost too rapidly, in fact, as Apple struggled to keep pace with the orders. But with Apple well in front of other players, temporary shortages only served to reinforce the cachet of the company's hot new innovation.

### AN APPLE A DAY FOR THE PHARMA INDUSTRY?

How does the pharma industry leverage the lessons from payback to continue bringing innovative medicines to the world while keeping shareholders satisfied? Given the backdrop of skittish investors and ill-tempered payers, the challenge is undeniably more difficult than it used to be. First and foremost, pharmaceutical executives must appreciate the primacy of cash—and the compound effects of time and risk on the payback equation. The inevitable conclusion is that companies must reduce the depth and duration of the cash-flow trough, hasten the eventual revenue build, and keep downstream costs to a level supportable by future market prices. In other words, they need to manage their companies to maximize cash flow—which is a tall order for an industry that attempts to balance current and future sources and uses over a 20-year cycle.

Nevertheless, the *iPod* example offers an illustration of how innovation and payback can be managed from end to end. Advances in genetics and biomarkers should make this increasingly possible in the pharma sector, though it will require a change from the current practice of one-shot learning. Due to functional silos and the highly structured regulatory development process, most companies have a tendency to compartmentalize decisions. Development organizations need to look beyond their traditional goal line of regulatory approval; the combined R&D and commercial organizations need to see access and reimbursement as equally important. As a result, very little attention is paid to continuous feedback throughout the entire business system.

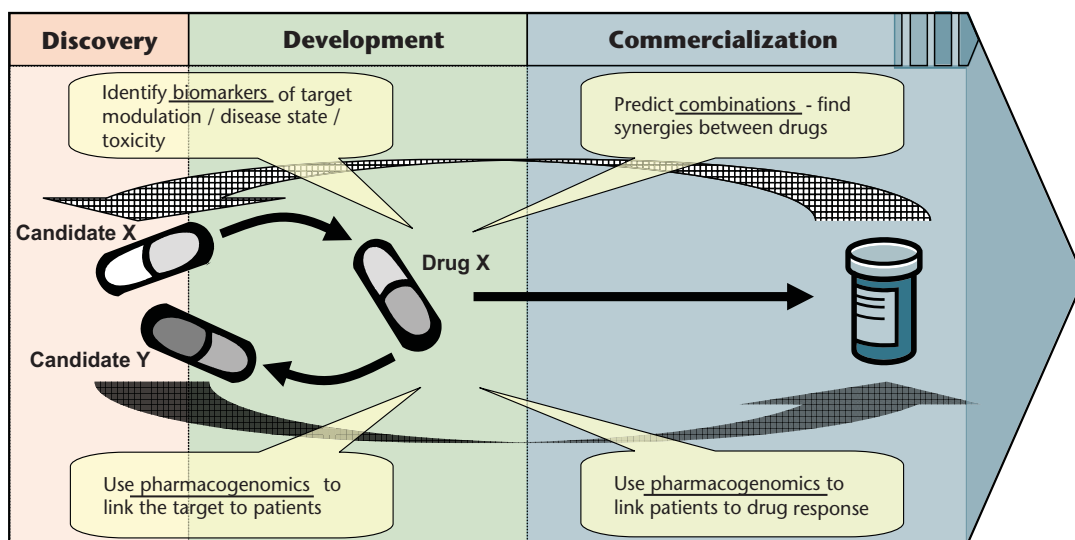
The problem is that most diseases are complex and their causes multivariate. Eureka moments occur, to be sure, but the learning process is usually more incremental. As the product makes its way through the new product development and commercialization process, pharma companies glean information about the target and disease pathway. By taking that learning and feeding it back into the discovery research group, companies can more quickly and confidently develop back-up products that incorporate their full knowledge about the disease or pre-

dict future product combinations that should have great efficacy for certain subpopulations. Clearly, this requires a set of capabilities, such as biomarker design and both predictive and correlative pharmacogenomics that are in formative phases at most companies. However, if companies can get this “closed loop” model working, the investment in underlying capabilities could cut the cost and time spent in discovery and development. With a shallower trough at the outset of the pharma cash curve, pharma companies could then generate stronger payback on downstream sales.

Lastly, the pharmaceutical industry features extraordinarily high intellectual content. Under traditional business and IP management systems, secrecy and hoarding of knowledge made absolute sense. In the information age, however, knowledge travels on a keystroke to distant scientists, patients, and other stakeholders. Although this presents a threat to pharmaceutical companies, it offers a compelling opportunity as well. What is needed is a pharmaceutical model that not only copes with information mobility, but actually thrives on it. For instance, Google, named the #2 most innovative company in the *BCG/BusinessWeek* poll, has excelled at attracting, motivating, and harnessing the creative talents of the world's top software engineers and mathematicians with its open

Exhibit 4

### The Closed Loop Model for Pharmaceutical Innovation



SOURCE: The Boston Consulting Group

architecture model. Some pharma companies are exploring open models. For instance, **Eli Lilly & Co.** executive Alpheus Bingham, PhD, co-founded and serves on the board of InnoCentive, an open source matchmaking company that connects “seeker” companies willing to pay a bounty to “solvers” who find the solution to certain technical puzzles. So far, however, no company has managed to make the process a mainstay of its business processes.

The pharmaceutical industry has always been a hotbed of innovation. Scientific discovery is sure to continue. What is less certain is how well that innovation will be turned into cash as the world’s capacity and desire to pay is increasingly challenged. The good news is that the remedies are coming into focus. Today’s pharma companies need to look to the cash curve to identify ways to reduce the cash downstroke, increase the probability of technical success, and extend the use-

ful life of their products. There are a variety of ways to reposition companies, but the wiser pharma players are getting on with it today to achieve payback tomorrow. **IV**

*In the March 2007 issue, we will address the issues the payback concept raises for medical device companies.*

*The authors are all Senior Vice Presidents and Directors with The Boston Consulting Group.*

COMMENTS: Email the author: [lawyer.peter@bcg.com](mailto:lawyer.peter@bcg.com)

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