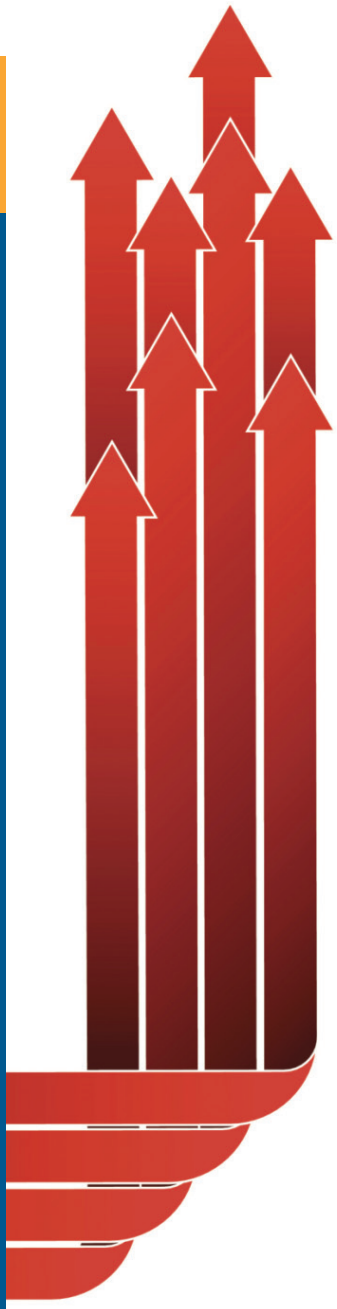
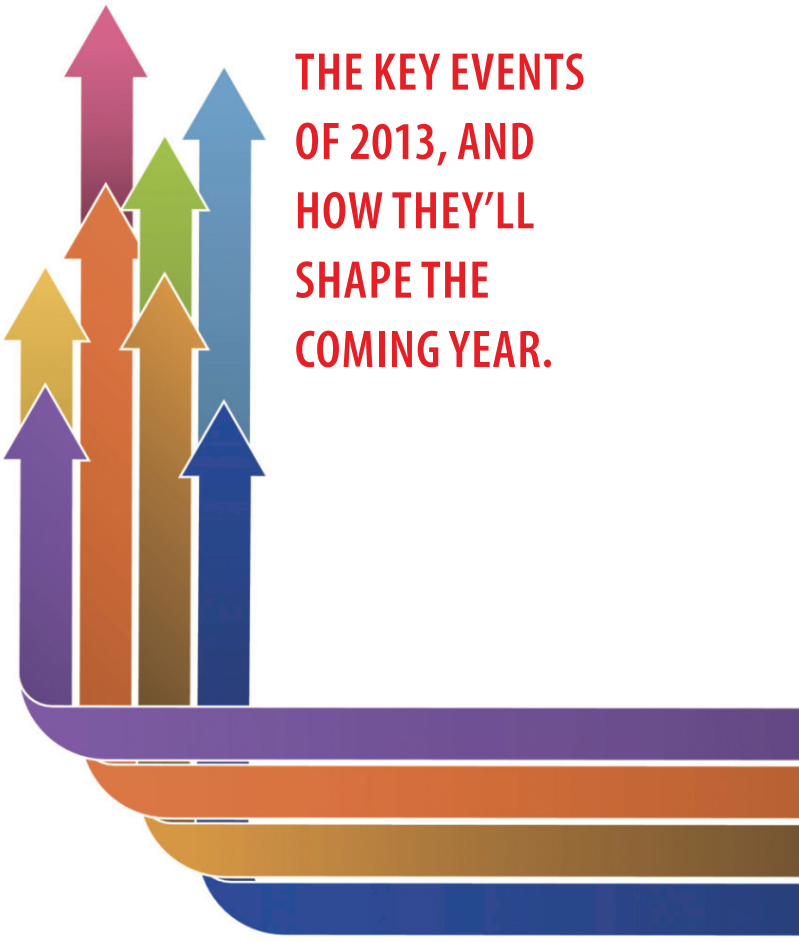
IN VIVO
THE BUSINESS & MEDICINE REPORT
www.ElsevierBI.com
JANUARY 2014 VOL. 32 / NO. 01

INSIDE



2013 IN REVIEW



THE KEY EVENTS OF 2013, AND HOW THEY'LL SHAPE THE COMING YEAR.

BY IN VIVO'S BIOPHARMA, DIAGNOSTICS, AND MEDTECH TEAMS

What Can Biopharma Learn From Apple?

The restructuring of pharmaceutical R&D organizations has failed to address fundamental issues that afflict R&D across several industries. Most of this shortfall can be attributed to a dearth of effective leadership within the C-suites of the drug industry.

BY MARKUS THUNECKE AND MARK RICHMOND

- Attempts to automate drug discovery through the use of genomics and other technologies have failed; R&D is being refocused, reorganized, or externalized at a frenetic pace with implications for shareholders, patients, and health care systems.
- The hands-on leadership model exemplified by Steve Jobs and Apple or Larry Page and Google in high-tech or by storied pharmaceutical executives like Merck's Roy Vagelos, Genentech's Art Levinson, or Paul Janssen provides valuable lessons for today's struggling pharma companies.
- Boards and executive management with strong understanding of science and medicine are essential to reinvigorating drug R&D, and can be complemented by strategic and organizational principles including a more narrow focus and simple corporate structures.
- Putting these principles into action will not be easy due to their bootstrapping nature – changes will not only have to be driven from the top but also will require a shift in leadership's attitude or sometimes even its composition. Learning from successful models outside of the pharmaceutical space can be an important catalyst in taking the first step.

Executive Summary >>85

Among the drivers of the pharmaceutical industry's present difficulties is an overreliance on acquisitions to drive growth and alleviate poor R&D productivity. Many surveys have demonstrated that M&A typically destroys more value, in all senses, than it creates and this effect is most pronounced in R&D (where dis-economies of scale exist).

This is in turn exacerbated by poor scientific and technical understanding by top management. When a pharmaceutical CEO and chief operating officer don't come from the world of medical research, they often fail to appreciate the potential of breakthrough scientific advances. For example, in the 1980s and '90s, only a few visionary CEOs foresaw the impact of the new recombinant protein engineering technologies that led to monoclonal antibodies and other major advances in drug therapy. Pharma is an industry in which proprietary technologies play a large role in drug discovery and (thus) shareholder value creation. Companies that experiment with new technologies at just the right time can reap large benefits.

A prevailing more-is-better approach, sometimes abetted by mergers, has led to a lack of focus in R&D activities. Pharma R&D departments are often trapped in a vicious circle of chasing too many complex projects with too few resources. That compromises quality and increases failure rates.

Indeed, many observers have become very skeptical of the future prospects for biomedical innovation per se – it has become common to refer to the "broken" biopharmaceutical business model. As a consequence, the most innovative part of the pharmaceutical industry, namely discovery research, is under enormous pressure. Many companies seek a remedy by cost-cutting and increasing externalization. The so called search and develop models, in which companies use their insights to cherry-pick in-licensing or acquisition opportunities, preferentially at risk-reduced later stages, are increasingly popular.

Much of this push-back can be viewed as a compensatory reaction to the overpromising that occurred during the heyday of genomics in the early 2000s, when breakthrough therapies for all sorts of diseases seemed within reach. But the pendulum seems to us to have swung

too far. Large organizations still perform a lot of exciting science, but those advances have become buried in a flurry of reorganizations and strategic shifts. The effect is often an acceleration of the underlying organizational pathology. A 2009 study published in *Nature Reviews Drug Discovery* by Bernard Munos demonstrated that it is virtually impossible to increase NME output to more than one per year per company, irrespective of total spending. Fully unleashing the true innovation potential of the biopharmaceutical industry requires stronger leadership, accountability for results, less complicated management structures, and incentivizing true value creation. Success would both restore the tarnished reputation of the biopharmaceutical industry and have enormously positive benefits for patients and health care systems.

LEARNING FROM OTHER INDUSTRIES

The biopharmaceutical industry is the most research-driven of all industries. Probably for that reason, there has been a reluctance to look elsewhere for role models when it comes to examining R&D and its management. The argument usually goes that the scientific complexity and intensity is so much higher in biopharma (because it is a science-driven, not engineering-driven industry) that it is a unique case. But we propose that the solution to the industry's conundrum will not be found by considering biopharma alone – the industry must look outside itself, to other creativity-led organizations and industries. The pace of innovation and the importance of technology make the high-tech/computer and engineering industries interesting comparators.

Some companies are held up as paragons of innovation and creativity. None is more inextricably linked with innovation-driven growth than **Apple Inc.** Over the past decade, its products have time and again broken new ground, giving consumers "something they didn't even know they wanted" – first the *iPod*, then the *iPhone*, and then the *iPad*. Consequently, Apple has risen to become the world's most innovative and admired company while spending only a few percent of sales on R&D; much of its success has been attributed to its founder/CEO, Steve Jobs.

Whether Jobs as a leader should be viewed as a role model for other managers is a topic of hot debate among academics. For some, he is viewed as an "outlier" who possessed skills that fly in the face of accepted management thinking and should therefore not be held up as an appropriate role model. Without adding to that specific academic debate, our view is that some elements of the high-tech leadership model exemplified by Apple, **Google Inc.**, and other companies provide lessons that are highly relevant to addressing the shortcomings of the current innovation-driven biopharmaceutical model.

In addition, we have also reviewed these lessons in the context of some of the best-performing R&D organizations in the history of the pharmaceutical industry: **Genentech Inc.** until its 2009 acquisition by **Roche**, **Merck & Co. Inc.** in the 1980s and '90s, and the Paul Janssen Research Institute (now part of **Johnson & Johnson**) in the 1960s to 1970s.

The most interesting aspects arising from this perspective can be summarized as follows:

- **Top leadership with a high degree of technological understanding in addition to general leadership skills** – This rare blend allows managers to formulate an innovative and highly effective strategic vision. It is essential when coupled with the management of day-to-day operations.
- **A quest for great products and not incremental advances** – This is one of the most critical factors in Steve Jobs' leadership model and at the core of Apple's DNA. Putting great products before profits, not vice versa. Deeply embedding this into a company's culture can inspire decision-making and behavior in employees at all levels.
- **The courage to focus** – There is a famous story about Jobs and how when he rejoined Apple as CEO he slashed an overly complex portfolio to focus on just three or four big product ideas for the entire organization. Great products and the courage to focus go hand in hand – focus avoids dilution of effort and the weakening of critical capabilities.
- **Simple structures and clear accountabilities** – In the pharmaceutical industry, accountability for success (and failure) has often been lost in its highly matrixed and global organizations. The result is that people feel powerless because of the numerous layers and committees between them and decisions. When drug candidates don't progress the reasons are often hidden. Entire books can be written about the difficult relationship between marketing and R&D. In many high-tech companies, and especially at Apple, marketing was responsible for selling but not for telling product development which products to develop next. There are lots of anecdotes about the sheer impossibility of "seeing what is next" from a pure market perspective, but companies still invest considerable effort to align the two.
- **Strategic perseverance** – The success of Apple and its CEO can also be seen as one of perseverance: sticking with the task, even when the odds seem slim and changing course or folding the program altogether seem like an easy way out. As the biopharmaceutical industry has the longest innovation cycles of all industries, it requires more strategic perseverance in its approach to R&D. In reality, one sees a very different picture, as many companies are tied up in cycles of restructuring and the frequent changing of strategic direction.
- **Seeing the woods and the trees** – Steve Jobs was famous for his strategic vision but also for his attention to detail. It is something the Japanese call genchi genbutsu, or "go to the source and see for yourself." The attitude requires that management go to the shop floor level to see and understand what is actually going on as most value is created there.
- **A healthy disrespect for the impossible** – This principle stems from Google's Larry Page. A major driver in companies like Google and Apple is to tackle problems that were thought too difficult by others. Steve Jobs had his often-cited "reality distortion field" that continuously led him to seek projects with enormous challenges and potentially huge payoffs.

SENIOR LEADERS MUST UNDERSTAND THE SCIENCE

A technical understanding of the discovery and development of pharmaceuticals is one of the most important factors in what is arguably the riskiest and most knowledge-intense industry. Perhaps surprisingly to some, there

PHARMA'S TOP PERFORMERS

Janssen Pharmaceutica Inc. was probably the most productive R&D organization in the history of the pharmaceutical industry, as it was responsible for developing 70 drugs between 1955 and 1993 (among them fentanyl for pain, haloperidol for schizophrenia, and many other breakthrough therapies within CNS). Although acquired by Johnson & Johnson in 1961, its founder, Paul Janssen, was granted full autonomy for running his business.

Merck under CEO Roy Vagelos, MD, from 1985 to 1994 produced many breakthrough therapies, among them *Timoptic* (timolol) for glaucoma, Vasotec (enalapril) and Prinivil (lisinopril) for the treatment of hypertension and heart failure, Mevacor (lovastatin) and Zocor (simvastatin) for the management of cholesterol, and Proscar (finasteride) for the treatment of benign prostate enlargement. It also developed Recombivax, the first vaccine developed through recombinant technology that protects against hepatitis B infection. Roy Vagelos was one of the first to apply systematic targeting of molecules (enzymes) selected for their biochemical role in disease processes – thereby setting the standard for drug discovery for decades to come.

Genentech is widely regarded as one of the most productive and successful biopharmaceutical companies ever. Under scientist CEO Art Levinson the company developed several breakthrough cancer therapies such as *Herceptin* (trastuzumab) for breast cancer (the first example of personalized medicine), *Avastin* (bevacizumab) for various solid tumors, and rituximab for various forms of lymphomas. In 2009 Genentech was fully acquired by Roche, but to protect its outlier status, the research part of Genentech was not integrated into the Roche structure.

is a stark contrast between founder-oriented high-tech companies and biopharma with respect to its top leadership's understanding of the complexity of the industry's key value drivers.

Many senior leaders within the high-tech industry have an excellent technical background and are able to formulate a vision of where the industry is heading technologically and how their own company should be positioned. Steve Jobs, Bill Gates, Larry Ellison, Sergey Brin, Larry Page, and Eric Schmidt, PhD, are just a few leaders who understood their respective industries in detail and bottom-up. Interestingly the same characteristics can be observed in highly successful automotive companies and in most companies of the technologically oriented German "Mittelstand." Their senior leaders are often engineers who deeply comprehend the technological complexity of their products, their future potential, as well as their markets.

In stark contrast, many biopharmaceutical companies are run by senior leaders whose generic leadership skills fit excellently within the general manager ideal but who are not well grounded technologically.

As of January 2013, only three of the top 20 pharmaceutical companies were being led by CEOs with an educational background in the life sciences, and only one of those had had true R&D experience in industry. The same is true for many directors: only 25% of board members at the same set of companies had a life science educational background, and only 8% had had relevant R&D experience.

In spite of the almost universally held belief that the top leadership needs to consist of *managers*, not *scientists*, few would actually argue that science is not the key value driver of successful R&D and a prerequisite for developing a compelling strategic vision. Yet few put this into practice. Larry Ellison, Steve Jobs, Bill Gates, and others can all write software code, yet how many biopharma CEOs actually understand the difficulties of fundamental bench-level research? The analogy in biopharma to writing software code would be to clone DNA or to synthesize a drug. How many CEOs can actually attempt that? The mere idea of this being relevant would most likely cause amusement in the industry. Even venture capitalists who have funded tech-driven biotech start-ups often exchange the initial founder-scientist CEOs of their companies with lawyers, accountants, or finance people. Scientists are usually highly qualified in the eyes of VCs only if they have previously sold a company to Big Pharma. Naturally, there are examples of CEOs with pure business backgrounds who thrive and are great leaders of biopharma companies. However, these leaders do not shy away from immersing themselves in complex technological questions or teaming up with (and listening to) a strong head of R&D.

A company that many biopharma industry executives view as a role model and a positive outlier in terms of innovation and R&D productivity is Genentech, especially during the period up to 2009 when it was still an independent company (it is now fully owned by Roche, but to protect its R&D outlier status the research part has never been fully integrated). One of our hypotheses is that Genentech's stellar performance is closely related to its leadership team's unique experience and understanding of the complex challenges of drug discovery and development, especially in oncology. Genentech's former CEO, Art Levinson, started out in 1980 as a bench-level scientist and rose through the ranks. When he became CEO he kept Genentech on its path as a science-driven company and oversaw its expansion from a pioneer in applying DNA cloning techniques to an oncology and biomanufacturing powerhouse. He saw much more potential in monoclonal antibodies than a lot of less-tech-savvy CEOs of large pharmaceutical companies, who by staying on the sidelines were forced to strike expensive licensing deals or acquisitions after firms like Genentech pioneered the technology. As CEO, he continued to be involved in project team meetings and in R&D discussions as a peer-to-peer participant. Perhaps not by coincidence, Art Levinson became a board member of Apple and a friend of Steve Jobs. He is currently chairman of the Apple board.

Lest we be misunderstood, requiring leaders to fully comprehend the key value drivers does not mean that essential business skills should be neglected. After all, a biopharmaceutical company is not a university. We point instead to that rare blend of scientific and technological skill with strategic vision and organizational capabilities embodied in, for example, Levinson and Vagelos. Ideally, leaders with similar profiles are needed to drive forward the biopharmas of the future. It is exceptional for a single executive to possess

that combination of rare skills. But it is entirely possible and desirable that a company's senior executive team and board should have sufficient complementary depth as a group. In addition, a CEO or chairman with a pure business background must allow himself to be influenced profoundly by technologically savvy visionaries.

THE QUEST FOR GREAT PRODUCTS

This is one of the most critical factors and should be part of the DNA of any innovation-driven company. The best illustration is again provided by Steve Jobs' mantra of always putting the quest for great products before profits. The logic is simple and motivating for most people: focus on generating truly great products and profits will follow. If you do it the other way around, mediocrity is the most likely result. It is the same philosophy that can still be found in many companies, large and small, particularly in Silicon Valley and even in the pharma industry, for example, during Vagelos' Merck tenure.

With today's double-digit price increases for specialty drugs, it may sound strange that Merck once tied its prices to increases in the consumer prices index. Interestingly, similar thinking also shines through in the famous "credo" of Johnson & Johnson, which dates back to 1943. Although J&J sometimes struggles to adhere to its own credo, it nevertheless serves as an essential glue that holds this highly diversified and decentralized health care conglomerate together.

For biopharma, it should be simple to put the quest for great products first since its primary raison d'être is the development of products that address unmet patient needs. Profits would then follow. Put into practice, this would be a highly ethical, if not noble endeavor. Although the "look and feel" of web sites and corporate brochures of many companies (especially in the US) reflect a focus on patient needs, dubious marketing practices and profiteering often completely undermine these sincere efforts.

Building a truly patient-focused organization is a largely untapped opportunity (although **Biogen Idec Inc.** is one example of a company that is aspiring to do so). The benefits could be enormous: not only the restoration of the industry's reputation but also the unleashing of creative reserves within large R&D organizations. Several studies in behavioral psychology have demonstrated that a sense of purpose is a much stronger motivational force than financial incentives. It is what Steve Jobs meant when he persuaded John Sculley to join Apple from **PepsiCo Inc.** by asking him whether he wanted to sell sugar water for the rest of his life or help change the world. (The same John Sculley was later responsible for Apple's demise as he shifted power from product development to marketing and sales – a fatal mistake in Steve Jobs' view not only for Apple but for all companies in general.)

The comparably long innovation cycles of the biopharma industry compared with high-tech raises barriers to finding great products quickly. Successful innovation requires very long-term vision and perseverance, but primarily because of short-term pressures, most companies seek "quick fixes" to keep investors happy. While this is economically understandable, the pendulum has swung too far. A large proportion of the products that make up biopharma pipelines today do not aim at major advances by addressing unmet patient needs. Instead, they are primarily directed toward retaining market position in established franchises. These products often come with little or only marginal differentiations and as a consequence require huge marketing efforts for their commercial success.

A large proportion of the products that make up biopharma pipelines today do not aim at major advances by addressing unmet patient needs. Instead, they are primarily directed toward retaining market position in established franchises. These products often come with little or only marginal differentiations and as a consequence require huge marketing efforts for their commercial success.

A large part of the reason for this lies in the very systems that are supposed to evaluate and incentivize those responsible for creating the products. Typically, the main metric for evaluating scientists and clinicians is based on counting the number of candidates or studies generated within a given time frame. This focuses effort purely on process, rather than encouraging originality. The quest for great products as a mind-set thus requires very strong leaders who accept no compromises when it comes to focusing on true innovation, even if it implies throwing out those incentive systems that many senior executives have come to rely on in the absence of any other metrics for judging short-term performance of R&D. To be fair, an increasing number of senior R&D leaders have realized this, examples include Marc Fishman, MD, at **Novartis AG** and Moncef Slaoui, PhD (and his predecessor Tachi Yamada, MD) at **GlaxoSmithKline PLC**. They were the first to implement science-driven models within Big Pharma, in which the quality of the science and the likelihood to address an unmet need in a differentiated way were more important than purely financial considerations, especially in research and early development.

Culture is an essential element in understanding why some companies are more hungry than others. This is ultimately what turned Apple into the world's most valuable company. Steve Jobs alone would not have been successful without building a culture of innovation at Apple. Changing culture implies winning over the hearts and minds of the thousands of highly educated scientists, clinicians, and other professionals who make up a large R&D organization. Many such individuals in biopharma today have been jaded by frequent restructuring and layoffs. But today's biopharma capabilities and potential are more advanced than ever. To tap into this resource will require a step-

change in leadership and direction setting, not just a reliance on current scientific and technological progress.

THE COURAGE TO FOCUS

Walter Isaacson's recent biography of Steve Jobs contains an anecdote that may serve as an illustration of what it really means to focus on critical projects. At an annual off-site strategy meeting, Jobs' group of managers struggled to create a list of Apple's top 10 priorities. It was difficult to choose from the various projects that were discussed. In the end, Jobs crossed out the bottom seven and announced that "we can only do three."

Within biopharma, R&D portfolios are often too large to be fully understood by any one person. While Genentech during its golden age had a relatively small portfolio of projects that could be fully grasped by the executive team, the typical Big Pharma portfolio today may contain 100 or more development projects. It is therefore no wonder that there are dis-economies of scale in R&D. Companies have simply become too large to be managed effectively – the recent trend to break down into smaller, more agile units ("the biotechization of Pharma") is a step into the right direction, but ultimately these units still operate within the bureaucratic governance system and culture of large parent organizations.

Maintaining the creative spark and entrepreneurial mind-set is difficult within outsized R&D organizations. The common centralized or committee-driven decision-making usually leads to a situation where people have to decide about projects without a proper understanding of the details. Sometimes, the most polished *PowerPoint* presentation/presenter wins, not necessarily the case for the greatest product.

Achieving true focus takes courage, especially in the risky biopharmaceutical industry, where many factors are beyond the control of management. These factors include poorly understood disease hypotheses and the enormous clinical and technical risks that can result in failure anywhere on a drug's journey from the laboratory to market. Because of this, many companies have shied away from focusing too much, because in a risky world; creating many "shots at goal" appears to be the best strategy. And there is always the fear that one could have been wrong in stopping a project too early. If resources and critical mass were sufficient, having a diverse portfolio would clearly lower overall risk of failure, but the problem is that resources are often insufficient to develop all projects to the same extent and with the same attention to detail. Couple this with aggressive process productivity goals and one gets a dangerous mixture from which many companies have suffered. Whereas R&D people are usually aware of this unhealthy dynamic, it takes a very strong senior manager to change the elements that were considered best practice only a few years ago.

Our own analysis of R&D productivity shows that the sweet spot seems to be an R&D budget between $1 billion and $2 billion. It is a fact that even successful R&D organizations don't scale up well. The million dollar question is what kind of model will enable today's outperformers like Biogen or Gilead to grow without losing their creative and productive edge?

Nevertheless, some companies have succeeded by only focusing on one or a few areas, and perhaps not by coincidence these have performed better than most. **Gilead Sciences Inc.** focuses on virology, **Celgene Corp.** on oncology, **Novo Nordisk AS** on diabetes, Biogen Idec on MS. All these companies have outperformed their less focused Big Pharma counterparts in R&D productivity (based on a Catenion study of R&D productivity measured as value of pipeline + products/cumulative R&D investment of the last 10 years, adjusted for cost of M&A). (*See "Gilead, Celgene, Biogen Head List Of Most Productive Biopharmas" —* "The Pink Sheet," *December 2, 2013.*)

The right leadership plays a strong role in achieving such focus. At Biogen it took CEO George Scangos, a PhD and former CEO of **Exelixis Inc.**, to uncover the science-driven culture and portfolio discipline that made it great in the first place. At Gilead, both CEO John Martin and chief operating officer John Milligan are PhDs with a strong track record in virology as well as business. John Martin's tenure as CEO has been long enough (since 1996) to at least partly attribute the current success of Gilead to his leadership. In addition to these recent examples, when Art Levinson first became CEO of Genentech he drastically reduced the size of its R&D portfolio by 75%.

Increasing focus also greatly increases the risk of catastrophic failure. Having a diverse portfolio has many benefits, but too often this argument is overstretched and used to disguise poor portfolio management. As most companies are already very diverse at many levels (disease areas, therapeutic modalities such as small molecules or antibodies, and scientific approaches), the main challenge is to define the appropriate selection criteria for choosing areas in which critical mass and deep capabilities can be established.

There are many benefits of a multi-factorial and fact-based approach when coupled to strong decision-making. However, focus requires a team of strong leaders and an equally strong clinical or technological vision. The problem with management structures in most R&D organizations is that they are overly complex and contain too many redundant checks and balances. In some cases, it seems that alignment has become a self-serving activity in which project information is usually aggregated over several levels until a few "politically correct" bullet points finally reach the CEO or top management body.

In our view, one empowered committee should be enough to steer R&D activities, provided the size of the portfolio is manageable. Our own analysis of R&D productivity shows that the sweet spot seems to be an R&D budget between $1 billion and $2 billion. It is a fact that even successful R&D organizations don't scale up well. The million dollar question is what kind of model will enable today's outperformers like Biogen or Gilead to grow without losing their creative and productive edge? **Pfizer Inc.**'s strategic options can be viewed in the same context – one could argue that it is a sheer impos-

sibility to re-instill the creative spark into its R&D organization without a massive change (such as a breakup).

SIMPLE STRUCTURES AND CLEAR ACCOUNTABILITIES

As illustrated in Adam Lashinski's 2012 book *Inside Apple*, at Apple, every senior manager is fully accountable for his function. Financial decisions are taken by the finance group, product development decisions are taken by the development group, and so on. In stark contrast, in today's biopharma world, the typical structure is a multidimensional matrix (e.g., functions, therapy areas, regions/sites). Truly focused accountability rarely exists.

Over the last few years, the "big step forward" in many organizations has been the early consideration of marketing – leading to market-driven target product profiles, peak sales forecasts, or net present value calculations for early-stage candidates. The problem with too much marketing input into early R&D is that it is inherently difficult to predict the potential of emerging technologies or products – this sometimes leads to marketing seeing little or no potential for early R&D efforts.

Of late, in some companies there has been the trend either to remove marketing input from early stages or to integrate it into R&D. At Apple, based on Steve Jobs' famous disregard for market research and focus groups, product development has been responsible for coming up with new products and marketing has been responsible for strategies for selling – very "old school," but effective. Injecting a dose of simplicity would do a world of good in the biopharma industry. One does not want a company full of functional silos – but it is a misperception that clear accountabilities lead to silo mentalities. Ultimately, marketing depends on R&D to be successful; and R&D depends on marketing to sell products and create positive cash flow for reinvesting into R&D. If the incentive system and culture capture the "one company" perspective and the top leaders re-enforce that, collaboration becomes a necessity.

Interestingly, Genentech and **Boehringer Ingelheim GMBH**, both highly successful, have had comparably simple structures, and in the case of Genentech, the company even deliberately decided against expanding its R&D footprint beyond South San Francisco. Genentech's leadership was concerned that the potential loss of the campus-like atmosphere and direct communication paths would outweigh the benefits of a global footprint. At Boehringer, the company for decades has followed a simple, functional setup, with R&D clearly in the driver's seat in terms of portfolio decision-making.

STRATEGIC PERSEVERANCE

The pace of progress, particularly in the scientific areas relevant to drug discovery, is tremendous. Today's common wisdom is often outdated in a year. This unique mixture in biopharma of extremely long fundamental innovation cycles and the explosion of scientific knowledge leads to the specific requirement to be both persistent and flexible at the same time. This is only contradictory on the surface. Persistency requires that a strategy is given an appropriate time frame in which it can play out – typically the fundamental innovation cycle in pharma take 20 years or more from first technological invention to full market impact (as in the case of monoclonal antibodies). Under such circumstances, changing the strategic direction every three to five years, in line with the average lifecycle of a CEO or research and development chief, creates a situation in which strategies are never fully implemented. But due to technological progress one needs to continuously create access to potentially relevant new technologies. The trick is to achieve that without going through major shifts in the fundamental direction and organization of a company. Instead of massive investments into emerging technologies (like Merck placing a huge bet on siRNA by buying **Sirna Therapeutics Inc.**), companies can create small-scale investments to enable access once a technology has matured to a degree where a full integration makes sense (an uptick in corporate venture capital and option-based dealmaking are recent examples).

Highly successful companies such as Boehringer Ingelheim or Novo Nordisk are shielded from too much short-termism because they are family-owned (Boehringer) or trust-owned (Novo). One could argue that Genentech's success can also be attributed to a patient majority shareholder (Roche), which shielded the company in a similar way for many years of perseverant investment into R&D. The company was at several points during its history heavily criticized by Wall Street for spending either too much on R&D or on specific projects like Avastin – but not having to fear a board revolt has surely helped them stay the course. The polar opposite of this approach can be observed in many contemporary biotech companies whose investors are pushing for a fast sale of the company or its assets. The lack of strong leaders with compelling vision has led investors to hire management teams whose main qualification is that they have previously sold off a biotech company to a large biopharma. These investors typically lack any real interest in helping companies develop great products – they first and foremost worry about a quick and lucrative exit. It is quite the opposite of what a Steve Jobs would have done. Of course, there are notable exceptions of companies with a long-term approach to funding innovation, and the best VCs/PEs play an important role in the biomedical innovation system; firms such as Sofinnova, OrbiMed, or MPM Capital come to mind.

SEEING THE WOODS AND THE TREES

One of the most critical capabilities, especially at the top management level, is to have both the ability to see the big picture and to dig deep into the key value drivers. The standard management textbook approach would be that top management should delegate many detailed tasks to specialists and focus on the big strategic topics. Managers who don't follow that rule are often condemned for unhealthy micromanagement. On average this may be true, but why is it then that most great leaders and visionaries tend to have an obsessive attention to detail, usually when it comes to the key value drivers of their respective businesses?

In many cases, including Jobs', this attention to detail stems directly from a strong intellectual curiosity and the fact that these individuals tend to really care deeply about what they are doing, and have the equipment to do it – the genchi genbutsu.

How many biopharma R&D leaders, let alone CEOs, have recently visited a laboratory and talked to their bench-level scientists? Most likely, senior leaders interact with the working level primarily during town hall meetings or when a scientist gets to present to a committee. And how many CEOs are capable of understanding what their bench-level scientists are actually doing?

Paul Janssen's management style is described in an excellent 2007 paper by Paul

Lewi and Adam Smith titled "Successful Pharmaceutical Discovery: Paul Janssen's Concept of Drug Research." Janssen knew about all the projects that were on-going in the company and also frequently went into the laboratories to ask his scientists, "What's new?" He strongly believed that continuous critical questioning from the top was a key to success. The result of such behavior, when displayed by somebody who is respected by the organization for his fundamental understanding, is twofold: it demonstrates that top leadership values the level at which most innovation is actually created and it instills a sense of urgency and quality control, because nobody wants to "look bad" in front of a Steve Jobs or a Paul Janssen.

"Management by walking around" can be traced back to Abraham Lincoln checking his troops in the Civil War. Although a useful management practice, it captures only a part of what is needed. The main difference is that Steve Jobs or Paul Janssen knew a lot about the objects of their inquiry. They were respected not only for their position but also because of their vision and insight. Interestingly, leaders who fit such a profile are not necessarily anti-hierarchical. Quite the contrary, as they do not shy away from using their authority to make decisions. But these decisions are deeply grounded in what is actually going on in projects at the working level, and do not rely on highly polished PowerPoint presentations. And for that, they are often better.

Too much specialization and attention to detail, without the ability to synthesize and recombine across epistemological and organizational boundaries, only creates incremental advances. Assembling different pieces across disciplines is most powerful if applied in combination with the traits discussed above. Classic management theory clearly emphasizes this skill for top management over "attention to detail," but we are arguing that the two are really complementary and equally important. Highly creative individuals can see both the "woods and the trees." These traits have also been described as a T-shaped profile by Tim Brown, the CEO of IDEO – a leading design consulting firm: "to know everything about a little thing, and to know a little bit about everything." Many breakthroughs are based on the recombination of pre-existing elements across boundaries, and in the biopharmaceutical industry there are numerous stories of serendipity leading to the development of major drugs. In spite of this, many companies have done their best to systematically eliminate serendipity in their monolithic "Center of Excellence" structures.

Let's assume you had some personal money to invest in solving a large pharmaceutical problem, such a finding a truly effective intervention for Alzheimer's disease. Would you give your money to one of the experienced and established biopharma players in the field, or would you bet on a new approach like Google/X-Labs?

A HEALTHY DISRESPECT FOR THE IMPOSSIBLE

A frequent criticism of the pharmaceutical industry is that it is shying away from the really big and difficult problems. It mostly stands on the sidelines waiting for "technological validation" before joining the playing field.

To be fair, companies have become cautious for good reasons, as billions have been spent on technologies with great promise that have never delivered. At the end of the 1990s, it was a common belief that genomics would deliver new drug targets, causally linked to chronic diseases, and that these drug targets could then easily be exploited with high-throughput screening and advances in medicinal chemistry. These advances, it was thought, would revolutionize biopharmaceutical R&D, creating more predictable "drug discovery engines."

This reductionist approach has obviously not delivered its promised breakthroughs. A detrimental side effect of this experience is the high degree of risk aversion (pessimists call it realism) that we observe today in large companies (and also among many biotech investors). Technologies that may actually lead to breakthroughs in the long term, such as gene therapy, stem cell-based therapies, therapeutic vaccination, or "systems biology," often play an insufficient role in the discovery work of large R&D organizations. It has to be accepted that such advances may take a long time to reach fruition in the form of novel products with market potential.

In spite of all the technological advances, the prevailing paradigm of drug discovery today can be traced back to the "key-lock" principle of Emil Fischer (1852–1919) and the receptor theory of Paul Ehrlich (1854–1915). Of course, there has been much progress since then, but in essence most organizations follow a very similar approach to drug discovery. At its heart is the belief that diseases can best be treated by blocking, activating, or modulating individual drug targets with highly specific molecules. Of course there are other approaches, such as enzyme replacement therapy or phenotypic screening (where Paul Janssen was a master), but especially the latter is an exception in an otherwise highly reductionist paradigm. There is hope, however, as some softening at the edges of this paradigm can be observed as more combination therapies and bivalent or even trivalent antibodies are being developed (Jack Scannell's 2012 article in *Nature Reviews Drug Discovery*, "Diagnosing The Decline in Pharmaceutical R&D Efficiency," contains an excellent discussion of the topic).

We would argue that a significant advance in treating the complex, multi-causal chronic diseases that plague patients and exhaust the funding capabilities of health care systems requires a different approach and strong visionaries to make it succeed. Steve Jobs'"reality distortion field" is much needed in today's biopharmaceutical industry. Interestingly, Google's Larry Page, who came up with the "healthy disrespect for the impossible" slogan, is putting this into practice by rejuvenating an old approach to R&D pioneered by **Xerox Corp.**'s PARC. Google calls it X-Labs and it is tackling the really big problems. Page has set the expectations very high, aiming for exponential improvements, thereby ensuring that the solution will only be found outside of the beaten path. While many of the programs

that X-Labs tackle fall into traditional high-tech domains, interestingly they have also started projects in health care, beginning with molecular diagnostics.

For the sake of argument, let's assume you had some personal money to invest in solving a large pharmaceutical problem, such a finding a truly effective intervention for Alzheimer's disease. Would you give your money to one of the experienced and established biopharma players in the field, or would you bet on a new approach like Google/X-Labs? The question may have sounded far-fetched a few months ago, but reality is catching up with us faster than anticipated: in September 2013, Google hired Art Levinson as CEO of **Calico**, a new company it is funding that is focused on diseases of aging. Calico recently announced a handful of senior hires, including Hal Barron as its head of research and development. Barron joins Calico from Genentech/Roche, where he was chief medical officer and head of global product development.

MOVING FORWARD AMID THE RESISTANCE

We have seen these principles and ideas, adopted from some of most innovative and visionary high-tech companies, fundamentally change the performance dynamics of pharmaceutical R&D, exemplified by companies such as Genentech, Janssen Pharmaceutica, and Merck. This, of course, is of utmost importance to shareholders of pharma companies. More important, it is critical to health care systems, especially in countries that will be hit the hardest by the medical infirmities of their aging populations.

Unquestionably, the most difficult aspect of effecting these changes is the "bootstrapping" nature of what is required. These principles go to the very heart of company's leadership models – affecting the composition of the board and executive management teams. Putting in place the right leadership team is the starting point. The leadership profiles and characteristics are in contrast to the reality at a lot of companies. As a result, implementation will have to start with a good dose of self-reflection if not soul-searching at the top. The other critical element is the realization that pharma can benefit from taking an outside-in approach to solving its R&D problems. Elements that have enabled other highly creative companies such as Apple or Google can have a profound impact within pharma, if approached with an open mind.

There is no doubt therefore that the process will take time and involve unsettling steps. But a change in mind-set and culture needs to take place, driven from the top by supervisory boards, investors, and key shareholders, and driven from the bottom by those professionals who are already in the biopharma industry first and foremost because they want to develop great drugs that really help people.

A#2014800006 IV

*Markus Thunecke, PhD (*markus.thunecke@catenion.com*), is a senior partner of Catenion, a boutique life sciences management consulting firm. Sir Mark Richmond, PhD, is an advisor to Catenion, a former member of Genentech's board of directors, and a retired R&D executive; most recently he was head of global research at Glaxo Wellcome.* *The authors would like to thank Arthur D. Levinson, Franz Humer, Masafumi Nogimori, Fred Hassan, Melanie Lee, Wolfgang Plischke, Vincent Aurentz, Annalisa Jenkins, Philip Brown, and the members of the Catenion team for invaluable feedback feedback on the manuscript.*

RELATED READING

"Gilead, Celgene, Biogen Head List Of Most Productive Biopharmas" — *"The Pink Sheet,"* Dec. 2, 2013 [A#00131202012]

ACCESS THESE ARTICLES AT OUR ONLINE STORE
www.ElsevierBI.com