OUTLOOK

The case for entrepreneurship in R&D in the pharmaceutical industry

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Abstract | A lack of entrepreneurial behaviour has often been highlighted as a contributor to the decline in the research and development (R&D) productivity of the pharmaceutical industry. Here, we present an assessment of entrepreneurship in the industry, based on interviews with 26 former and current leaders of R&D departments at major pharmaceutical and biotechnology companies. Factors are highlighted that could be important in promoting entrepreneurial behaviour, which might serve as a catalyst for revitalizing R&D productivity.

Large pharma is in trouble, but is essential for the success of the industry. Tadataka 'Tachi' Yamada, President, Global Health Program, Bill and Melinda Gates Foundation

The pharmaceutical industry is currently facing the key challenges of declining R&D productivity, higher barriers to commercial success for innovative drugs and substantial imminent losses of revenue from successful products due to generic competition. For example, it has been estimated that for every US dollar of revenue lost from established products by the largest pharmaceutical companies as a group between 2007 and 2012, only 26 cents will be replaced by revenue from new products[1].

Awareness of these challenges has catalysed — and continues to drive — considerable reorganizations in the R&D structures of large pharmaceutical companies. Among the goals of such reorganizations has been the promotion of the type of entrepreneurial culture and behaviour that is considered to thrive in smaller biotechnology companies[2] in the hope that this will increase R&D productivity. Indeed, industry observers have attributed some of the present crises in the pharmaceutical industry to the discouragement of entrepreneurial behaviour by limitations inherent in the unwieldy bureaucracies that can proliferate in large pharmaceutical companies[3].

Given that the R&D departments in large pharmaceutical companies in theory provide strong platforms for innovation and thus competitive advantage, we therefore sought to investigate three interrelated questions about the potential for entrepreneurship in such companies. First, to what extent is there evidence of entrepreneurial behaviour in large pharmaceutical companies? Second, can the entrepreneurial behaviour characteristic of small biotechnology firms coexist in the context of the large-scale and late-stage development activities typical in large pharmaceutical companies? And third, are there any lessons from the experiences of R&D leaders in such companies that could be used to inform the future development of corporate cultures in the pharmaceutical industry?

In an attempt to answer these questions, we first reviewed the relevant literature and identified some of the characteristics associated with entrepreneurial behaviour[4]. It must, however, be noted that there is a paucity of literature on entrepreneurial behaviour in industries with a prolonged cycle time between the application of new science and product launch, as is the case in the pharmaceutical industry. We chose to focus on three principal characteristics of entrepreneurs — which we termed vision, bias for action and winning attitude — and identified forms of behaviour corresponding to each category for both individual entrepreneurs and entrepreneurial organizations. Vision refers to the ability to see and the drive to realize the potential value of nascent ideas and technologies. Bias for action refers to a readiness to make and to implement decisions and to modify these actions as new information becomes available. Winning attitude is the propensity to see hurdles as manageable challenges and to treat what others consider failure merely as unwanted or unexpected outcomes.

Our research relied on open-ended interviews with former and present leaders of R&D departments in pharmaceutical and biotechnology companies (see BOX 1 for the affiliations of the interviewees and BOX 2 for the interview methods). Together, these organizations represented greater than 35% of the pharmaceutical industry output in 2007 (as measured in sales)[5,6]. In this article, we synthesize the findings from these interviews to highlight common themes and key factors that could promote entrepreneurial behaviour in the pharmaceutical industry, and thereby help to enhance R&D productivity.

Theme 1: fewer shots on goal

Success isn't necessarily how many shots on goal, but on betting on the high probability. It's fewer shots on goal. Phil Needleman, former Senior Executive Vice President and Chief Scientist, Pharmacia

Approaches to drug discovery that focus on the number of compounds, which were established in some companies from the late 1990s onwards, may have actually discouraged entrepreneurial behaviour during the discovery phase. "The 'compound progression model' [which focuses on the significance of attrition during each phase of development] might have rendered a major disservice to the biopharmaceutical industry," noted Yamada. "It took the industry away from innovation and pushed it to volume."

The consequence of this approach was a focus on portfolio management and on quantity instead of quality, and an emphasis on the production of new molecular entities (NMEs) at each stage. As Yamada explained, large companies were then evaluated and rewarded by analysts for the number of compounds in their R&D pipeline and,

more recently, for the number in the later phases of clinical development in particular. Similarly, research organizations in large pharmaceutical companies were rewarded for the number of NMEs produced as clinical candidates each year. As Corey Goodman commented, "scientists are getting their bonuses based on trying to make the numbers." However, with the exception of a sharp increase between 1996 and 1998, the number of NMEs approved annually by the US Food and Drug Administration (FDA) has not changed over the past five decades, even though the costs of achieving approval have increased many-fold during this period[7].

Interestingly, an assessment of the value of small biotechnology companies was driven by the innovation and science in the one or two products moving through their pipelines. As an example, Tom Glenn recounted the birth of DNase at Genentech, which was developed during a biweekly staff meeting in which research ideas were discussed: "He [Steve Shak, M.D.] brought in two test tubes. In one test tube, he had this gunky sputum. In the other test tube, he had this clear liquid. I'll never forget this. There were six of us sitting there watching. He mixed the contents of the two test tubes together, and they cleared. He said, 'Gentlemen, that's DNase.' Unbelievable. On the spot we decided to move forward and finish our discovery and development program in DNase, which is now a product marketed by Genentech."

The insidious consequence of the focus on quantity in large pharmaceutical companies has been an emphasis on the commercially driven evaluation of a portfolio of compounds, instead of the scientific merits of each compound. Mark Fishman similarly expressed scepticism regarding the deep involvement of commercial departments before the availability of clinical data from Phase II trials, when he stated: "Often, they would ask if you are 'aligned' with the business franchises. I don't want to be because they are looking at today, and I want to be there five to ten years from now. So, if we are aligned with the current business franchise, we are dead in the water."

Despite such scepticism, however, there are those scientists, such as Andreas Busch, who although not ignoring compound quality, remain practitioners of the compound progression approach, illustrating that innovation can coincide with less entrepreneurial-focused approaches. Peter Corr supports Busch's view, especially when there are "more shots on goal". However, Goodman thinks "that in many of these companies, too many drugs are being advanced into the clinic". And Needleman was of the opinion that "success isn't necessarily how many shots on goal, but on betting on the high probability. It's fewer shots on goal."

Box 1 | **Interviewees**

Our research involved open-ended interviews with former and present leaders of research and development (R&D) departments in large pharmaceutical companies and biotechnology companies. The sample of interviewees included the following individuals:

- Burt Adelman M.D., President of Research and Development at Eleven Biotherapeutics (2009–present), former Executive Vice President of Portfolio Strategy at Biogen Idec (2003–2006).
- Robert Armstrong Ph.D., Vice President of Global External Research and Development at Lilly Research Laboratories (2006–present).
- Lee Babiss Ph.D., Executive Vice President, Global Laboratory Services at Pharmaceutical Product Development (2010–present), former Global Head of Pharmaceutical Research at Hoffman-LaRoche (2007–2009).
- Joshua Boger Ph.D., founder and former President and CEO of Vertex Pharmaceuticals (1992–2009).
- Andreas Busch Ph.D., Head of Global Drug Discovery at Bayer Schering Pharma (2007–present).
- Peter Corr Ph.D., former Senior Vice President of Science and Technology at Pfizer (2002–2006).
- Frank Douglas Ph.D., M.D., former Executive Vice President at Aventis (1995–2004).
- Mark Fishman M.D., President of Novartis Institutes of Biomedical Research (2002–present).
- Tom Glenn Ph.D., former Vice President of Pharmaceutical Sciences at Genentech (1988–1990).
- Corey Goodman Ph.D., former Head of Biotherapeutics and Bioinnovation Center at Pfizer (2007–2009).
- Bernd Kirschbaum Ph.D., Executive Vice President of Global Research and Development at Merck Serono (2008–present).
- Jeff Leiden Ph.D., former President and Chief Operating Officer, Pharmaceutical Products Group at Abbott (2001–2006).
- George Milne Ph.D., former Executive Vice President of Global Research and Development at Pfizer (2000–2002).
- Phil Needleman Ph.D., former Senior Executive Vice President and Chief Scientist at Pharmacia (2000–2003).
- Garry Neil M.D., Corporate Vice President, Corporate Office of Science and Technology at Johnson & Johnson (2007–present).
- John Patterson Ph.D., former Executive Director of Development at AstraZeneca (2005–2009).
- Steven Paul M.D., former Executive Vice President of Science and Technology and President of Lilly Research Laboratories at Eli Lilly (2003–2010).
- Joerg Reinhardt Ph.D., Chief Operating Officer at Novartis (2000–2009).
- Peter Ringrose Ph.D., former President of the Bristol-Myers Squibb Pharmaceutical Research Institute at Bristol-Myers Squibb (1997–2003).
- David Rosen D.V.M., Executive Director and Head of Out Licensing, Worldwide Business Development at Pfizer (2007–2009).
- Leon Rosenberg M.D., Professor in the Department of Molecular Biology at Princeton University, New Jersey, USA (1997–present), former Senior Vice President of Scientific Affairs at Bristol-Myers Squibb (1991–1997).
- Robert Ruffolo Ph.D., former President of Research and Development at Wyeth (2002–2008).
- Vicki Sato Ph.D., Professor of Management Practice and Professor of the Practice in the Department of Molecular and Cell Biology at Harvard University, Boston, Massachusetts, USA (2005–present), former President of Vertex Pharmaceuticals (2000–2005).
- Ben Shapiro M.D., former Executive Vice President, Worldwide Licensing and External Research at Merck (1996–2003).
- Alan Smith Ph.D., Senior Vice President of Research and Chief Scientific Officer at Genzyme (1996–present).
- Gus Watanabe M.D. (now deceased), former Executive Vice President of Science and Technology at Eli Lilly (1994–2003).
- Tachi Yamada M.D., President, Global Health Program at the Bill and Melinda Gates Foundation (2006–present), former Chairman of R&D, GlaxoSmithKline (2001–2006).

Theme 2: smaller is better

I think the key is creating something which is close to a biotech company … within big pharma. Garry Neil, Corporate Vice President, Corporate Office of Science and Technology (COSAT), Group President, Johnson & Johnson pharmaceutical R&D

Several heads of research departments expressed the view that "small is better". Frank Douglas and Tachi Yamada each tried to reduce size and complexity in their companies. In 1998, Douglas introduced the drug innovation and approval (DI&A) organization at Hoechst Marion Roussel (now part of Sanofi-Aventis) in which each of the three discovery sites (one each in New Jersey, USA, Frankfurt, Germany, and Paris, France) was responsible for no more than two to three therapeutic areas through to Phase IIa, and a global development centre coordinated the late-stage development and regulatory submission activities. A product development committee determined which compounds would be further developed beyond Phase IIa by the global development centre.

Yamada introduced the Centres of Excellence for Drug Discovery (CEDDs) at GlaxoSmithKline. Each CEDD was responsible for one or two therapeutic areas through to Phase IIa trials. There was more autonomy in the CEDD, as compared to the DI&A, in that the only item that was centrally controlled was headcount. Recently, GlaxoSmithKline evolved the CEDDs into smaller subgroups, as they thought the CEDDs had become too bureaucratic.

There seems to be an inverse correlation between the size of an organization and its potential to develop trust among its constituents and facilitate the rapid exchange of data for the generation and testing of hypotheses. Joshua Boger and Vicki Sato described the focus of Vertex Pharmaceuticals as building a culture in which people are rewarded for making quality data rapidly available and ready for integration. "I think they [large pharmaceutical companies] have difficulty sharing information quickly … holding onto information can be a form of power … it is part of a behaviour pattern that contributes to things taking longer, costing more and creating redundancy," said Sato.

Confidence in the quality of data presented allowed departments to circumvent the wasteful practice of rechecking data because of a lack of trust in the expertise or in the care of those who initially generated the data. The accessibility of senior managers and their involvement in project status discussions is essential in reinforcing these principles of rapid exchange of quality data and testing of hypotheses, all of which are hampered as organizations increase in size. Boger and Sato also noted that as Vertex increased in size, much more time was required to build these cultural aspects. Sato added: "I went to every project team meeting and before I joined Vertex, Josh went to every team meeting. It allowed us as senior executives to lead by example and build the culture. You can do that when you are small."

However, with 200 to 250 researchers per therapeutic area, the DI&A and CEDD groups were still too large in the view of Goodman, who feels that "the optimum size of a discovery group is one in which all members could assemble in a modest-sized room and conduct a discussion without recourse to a microphone." Corr, who led groups at Searle, Parke-Davis and Pfizer, thinks that the optimal number is closer to 20 to 40 individuals operating as an autonomous group. Corr discovered that very small teams at Parke-Davis allowed for the rapid sharing of information and resource allocation, as well as the efficient termination of projects that would eventually fail. Yamada similarly talked about small groups being "agile and interconnected to the other person."

A recent experiment at Pfizer, known as the Biotherapeutics and Bioinnovation Center, which was led by Goodman and has since been dissolved, was focused on managing four to five independent small biotechnology companies in a network. In this arrangement, best practices could be shared and resources leveraged, but each unit remained autonomous and was to some extent free to advance its own culture. The head of each small company was therefore endowed with a sense of ownership and could more or less operate as an entrepreneur. According to Goodman, Pfizer wanted to see whether such 'skunkworks' strategies, similar to those used in the information technology and electrical engineering fields, could be harnessed to change the way compounds were typically developed. Neil also supports this view of the potential of small companies to produce changes within their respective larger corporate structures. He characterizes the culture at Johnson & Johnson as "a hybrid between biotech and large pharma" and attributes its success to the strategy of maintaining the cultures of newly acquired companies and adopting their best practices.

Contributing to the apparent consensus on behalf of the entrepreneurial potential inherent in smaller teams, Fishman offered his perspective on the importance of individuals in innovation: "To me, innovation is generally an individual effort. There is a person who sees something different, sees something new, has a clarity of vision, and the courage to pursue it. That individual expands to work in an entrepreneurial team to bring the innovation to fruition." Alan Smith expressed a similar view, noting that in his opinion it is indeed the "curiosity" of the individual scientist that is most often the driver for discovery efforts. Robert Armstrong, in commenting on CHORUS — a unit of 32 Lilly employees who comprise an autonomous entity he heads that conducts 'lean' development from the candidate selection stage to the proof-of-concept of selected Lilly compounds — said: "not all of them need to be serial entrepreneurs, but there are individuals who perceive radically different ways to develop new molecules and want to enable these concepts" (see also the section on middle managers).

Although many of those interviewed spoke on behalf of smaller and more entrepreneurial discovery units, Burt Adelman pointed out that such scale does not in itself necessarily engender the "sense of urgency" crucial to successful product innovation. He argued that entrepreneurial behaviour diminished even in biotechnology companies when the focus was primarily on publications rather than on products. In this context, he poses the difficult question of why scientists who have not been associated even with a failed drug after 6 or 7 years should still be employed by that company.

George Milne conceded the previously cited benefits associated with small size, but also presented an argument on behalf of larger corporate structures in which smaller units benefit from the experiences and tacit aggregate knowledge of the larger organization. Milne considers that the biopharmaceutical industry must learn to scale small entrepreneurial units without introducing excessive bureaucracy. Such units thus become empowered to unleash "random and purposeful action". Milne also noted that "one of the scale-based advantages that a large, entrepreneurial organization has over a small one is that you actually get to learn from experiences."

A comment from Jeff Leiden provides an eloquent if blunt summary to a consideration of the benefits associated with the deployment of smaller teams and the instinctive, curiosity-driven culture they foster: "So, it became clear to me that the way to organize R&D, and frankly I think the whole business, is in much smaller entrepreneurial units where people feel both responsible and accountable for producing or their unit won't be renewed. They know that their careers depend directly on their productivity."

Box 2 | **Study methods**

Before our interviews, we sent each interviewee our lists of behaviours that described both individual and organizational entrepreneurship and the following questions to serve as a basis for the interview:

General questions

- Did 'entrepreneurial' and 'big firm' characteristics fuel the growth of large biopharmaceutical companies ('big pharma')?
- Was or is there entrepreneurial behaviour in big pharma?
- Were there lessons that can inform new organizational paradigms to increase productivity?

Interview questions

- How would you describe your R&D organization when you assumed leadership?
- What were its strengths and weaknesses?
- What were some of the organizational changes you introduced?
- What did you hope to achieve?
- How did you balance individual recognition versus team recognition?
- What specific outcomes can you cite that were affected by the changes you introduced?
- What are the differences between today's challenges and those that existed when you were head of R&D?
- What would you do today to address those challenges?
- Did you create any special teams, spin-outs or collaborations to achieve your objectives?
- How did you access R&D knowledge from outside your firm? How has this changed in recent times?
- How did you balance your portfolio with respect to investing in long-term projects versus short-term projects?

The interviews were carried out by teleconference by F. L. Douglas and V. K. Narayanan and were taped with the permission of the participants. This process allowed us to focus on the interview and use the transcripts afterwards to improve our understanding of an issue or later send questions for clarification to the interviewees.

Theme 3: reward systems matter

I am firmly a believer that you get what you reward. Josh Boger, former CEO, Vertex Pharmaceuticals

In most industries, as companies grow, there is pressure for each to offer uniform compensation, rewards and benefits. Fishman and Goodman, as well as Peter Ringrose, each referred to the tendency for all departments to compensate in a similar fashion as a "homogenizing effect". What is curious is that although large companies recognize the need to implement special bonus systems to incentivize sale representatives to act 'entrepreneurially', the opposite occurs in R&D. The lack of incentives has persisted owing to organizational inertia, but thoughtful R&D leaders have begun to address this issue by instituting different evaluation and reward systems.

For example, Yamada observed that Sir James Black, who had the key role in the development of β-blockers and histamine blockers, never received a major bonus for his discoveries. As a consequence of this awareness, Yamada established a new reward system at GlaxoSmithKline: "I set up a program where once we had a proof-of-concept molecule, we'd form a team of the top scientists in the company. It was like a Nobel committee. They'd go back and research how was it we got here. If they could identify one or two or three people that were really the fundamental reason for the success of that molecule, then those people got an extraordinary deal." However, although Armstrong admits that they should find a way to reward the members of the CHORUS that might be different from the rest of R&D at Eli Lilly, he remarked: "In this experiment, this group, first and foremost, is hugely motivated, very energetic in large part because they're uniquely empowered to actually carry on a tremendous amount of work in the organization."

Theme 4: underutilized middle managers

I used to give a lecture, and still do, which is entitled 'The power of the light you shine'. George Milne, former Executive Vice President of Global Research and Development, Pfizer

The role of middle managers — defined as those individuals in large pharmaceutical companies who are not at the executive level, but who lead large groups or departments and have considerable responsibilities for the successful conduct of projects and programmes — emerged as an important concern in the productivity of discovery units, even more so than in the case of development. Milne observed that scientists become middle managers as a reward for their outstanding scientific contributions and often for their entrepreneurial behaviour. However, after they attain the status of middle managers, they are rewarded for productivity as measured by the number of compounds at the required phase, by achieving timelines and by performing activities that engender need for control and predictability, none of which might be the appropriate measures for discovery. Consequently, middle managers can become frustrated with this change in strategies. Milne motivated middle managers through his Hawthorne-effect-style lecture, reminding them that although they may not feel that important, the scientists working under them feel they are really important and, as a result, "could tell them where their light shines and where it doesn't."

As we probed the desired qualities that would facilitate the selection of middle managers most likely to foster entrepreneurial behaviour, Yamada, Ringrose, Sato and Douglas identified two discovery types, which we term 'mavericks' and 'true believers'. Mavericks are those scientists who, although they may share the goals of the organization, seem to achieve superior results by thinking and working outside the prescribed or routine organizational conventions. True believers not only are convinced of the scientific approach of their given project, but can also communicate and recruit organizational support and resources for the project — a particularly important quality, according to Sato.

Steven Paul, Armstrong, Boger and Fishman stressed the importance of middle managers retaining their scientific/technical edge if the company is to benefit from collaborations. Paul and Armstrong also described a series of approaches used at Eli Lilly to engage middle managers in entrepreneurial activities. They focused on the 'sourcing of innovation' as a means of getting their middle and senior managers to take ownership for finding the best solutions, regardless of where they were identified. Thus, Lilly was an early adopter of the practice of leveraging knowledge from outside the company for solutions to internal problems. This successful approach was later spun out as Innocentive. Lilly

also introduced the proof-of-concept unit CHORUS (see above), and in an extension of this concept, Lilly launched a joint venture with Jubilant Organosys in Bangalore, India, to develop molecules between preclinical and Phase II testing in May 2009. Through this collaboration, Lilly also benefits from the potential opportunity to have access to successful proof-of-concept compounds from sources other than their own research laboratories. Armstrong said that Lilly has expanded this concept to several companies in India and China, who work on selected compounds that Lilly has the right to buy back when predetermined milestones are achieved. "These activities dismantle vestiges of the 'not invented here' syndrome that can mean certain death to entrepreneurial behaviour," he noted.

Paul of Eli Lilly summarizes this more broadly: "So, one element of the transformation from a corporate perspective structurally is to go from this FIPCO (Fully Integrated Pharmaceutical Company) structure to a FIPNET, Fully Integrated Pharmaceutical Network. We've defined three levels of this FIPNET. Level one is more traditional outsourcing. Level two leverages partnerships with universities and small as well as larger companies. These value-sharing partnerships provide both risk sharing and cost sharing. Finally, a level three FIPNET or partial ownership model allows small companies to pursue projects within the context of their unique cultures."

Our interviews also suggest that discovery-stage collaborations are perceived to be effective when the collaborators share a common sense of curiosity and focus on science. The importance of 'curiosity' as a driver for the selection of technology, biological mechanisms and collaborations was stressed as a key component of the culture at Genzyme by Smith, who added that curiosity refers to a desire to learn and benefit from knowledge that others "in that university in India or in France" might deem interesting.

We determined that among the tasks that need to be performed at the middle management level are the maintenance of organizational knowledge, the nurturing of mavericks and true believers, and the provision of support for the drug discovery teams. Essential to these roles is the need to remain close to science.

One of the distinguishing characteristics of the biotechnology researchers we interviewed was their closeness to science and their desire to retain this proximity. In large pharmaceutical companies, however, excessive concern with milestones often detracts from the ability of research teams to remain close to science. Yet to the extent that the rewards system associated with middle management is based on the attainment of milestones and not on the nurturing of science, bureaucracy imposes barriers that are detrimental to drug innovation. Indeed, evolving a more sophisticated and nuanced reward system for middle management may be among the most important organizational priorities for large pharmaceutical companies to stimulate productivity in the crucial discovery stage.

Theme 5: CEO–Head of R&D interaction

You have to really be able to communicate with your CEO if you're going to do your job optimally in R&D. Gus Watanabe, former Executive Vice President of Science and Technology, Eli Lilly

Several of the interviewees, including Leon Rosenberg, Watanabe, Goodman, Milne and Glenn, stressed the importance of a close alignment between the CEO and the head of R&D in building and maintaining an optimal culture in discovery. Boger described building an innovative and productive organization as more of a social experiment than a technical one. He and Sato described in nearly identical terms their tireless and consistent efforts to build, nurture and maintain elements such as interdisciplinary teamwork, rapid access to information and a sense of ownership in their organization. Rosenberg described the weekly meetings that he used to have with the CEO: "He wasn't a scientist, but he appreciated science, and he liked scientists. He and I would converse regularly after he would read his weekly copy of *The New England Journal of Medicine*. This was a great joy of mine because it kept me very close to him. It allowed me to put science high in the order of his thoughts." Smith described similar efforts and alignment with Genzyme CEO Henri Termeer in maintaining their organizational culture. Busch and Bernd Kirschbaum gave examples of the considerable challenges and efforts needed to build a common culture in a newly merged organization and its impact on innovation, and the important role that alignment with their CEOs had in their efforts to build the desired culture in discovery. Douglas also commented on the importance of the close alignment between him and Richard Markham when they took on the task of building Hoechst Marion Roussel, the result of merging Hoechst Pharmaceutical, Marion Merrell Dow and Roussel Uclaf, in their respective roles as Head of R&D and CEO.

Theme 6: technology and R&D models

My major responsibilities as given to me by the CEO when I joined BMS were to forge a single R&D organization out of two groups with differing strengths in Discovery and Development. Leon Rosenberg, Professor at Princeton University and former Senior Vice President of Scientific Affairs, Bristol-Myers Squibb

The interviews revealed the unexpected finding that although each R&D leader recognized that changing science and technology influenced how they organized their research units, most had not reflected on the impact that organizational changes might have on entrepreneurial behaviour. The interviewees identified four types of organizational structures or models that defined the point at which commitment was made to the full-scale clinical development of a compound (FIG. 1).

First, they described a traditional R&D organization, in which the transition from research to development occurred with the filing of an investigational new drug application. This is termed the preclinical proof-of-concept (pPoC) model. The second structure mentioned — the human proof-of-concept (hPoC) model — was similar to this, with the addition of clinical pharmacology to improve dose selection and the search for efficacy in humans.

The third structure, known as the clinical proof-of-concept (cPoC) model, includes Phase I and Phase IIa trials in research. It uses biomarkers and pharmacokinetic studies to select the best compound to determine efficacy in the target patients, with efficacy in Phase IIa trials being the crucial decision point for full development (FIG. 1).

Watanabe, deceased since the interviews, introduced this concept by having M.D.s or M.D./Ph.D.s responsible for each discovery therapeutic unit from the concept stage to Phase IIa trials at Eli Lilly. Glenn introduced the 'clinical biology unit' concept in research at Ciba Geigy in 1984 with the goal of carrying out specific studies in patients to achieve proof of concept. Several other companies have adopted this model in various forms. These include the research and early development (RED) units at Johnson & Johnson, the research units at Merck-Serono, global drug discovery at Bayer Schering Pharma and disease biology areas at Roche (it should be noted that Roche's new focus on personalized healthcare by interweaving their diagnostic and pharmaceutical divisions has moved them to the fourth model;

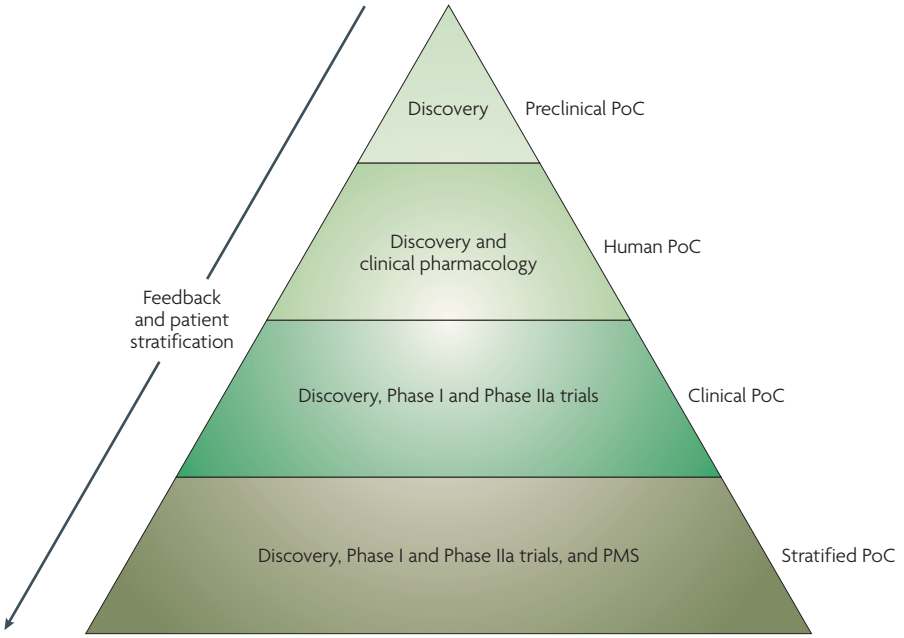

Figure 1 | **Evolution of discovery models to identify the 'right drug for the right patient'.** Four types of organizational structures for discovery research were identified on the basis of the point at which a commitment is made to the full-scale clinical development of a compound. The integration of activities needed to identify 'the right drug for the right patient' is catalysing a transition towards the stratified proof-of-concept (PoC) model, which allows active feedback between discovery, research, Phase I and Phase IIa trials, and post-marketing surveillance (PMS).

see below). The formation of the Novartis Institutes for Biomedical Research (NIBR) has served to institutionalize this practice, and to implement the fourth model (see below).

Present interest in the potential of translational medicine to find 'the right drug for the right patient' requires the integration of several activities. These include the search for biomarkers that not only help to select compounds preclinically, but also help to predict, stratify and monitor the patients and subgroups who will experience the requisite efficacy of the compound and an acceptable level of adverse events. To achieve this, collaboration between research and post-marketing surveillance groups is necessary. The increasing focus on adverse events, which often have a low frequency in the preregistration trials (Phase IIb and Phase III), argues for the fourth organizational model: the stratified proof-of-concept (sPoC) model (FIG. 1). This structure allows active feedback between discovery research, Phase I and Phase IIa trials and post-marketing surveillance, and includes the potential development of biomarkers to identify those patients who might be more likely to experience adverse events. There are instances with such models in which a change in the administration regimen of the drug or the selection of an alternative drug has provided greater benefit to particular patients.

The impact of structure on the type of organization is probably best understood by some historical examples. In 1987, Pfizer was an early adopter of the 'clinical biology unit' concept, in which the focus was on identifying markers of disease and human models of disease that would rapidly determine whether, and in which patients, novel mechanism-based compounds would be efficacious. However, the traditional R&D structure at Pfizer, in which the transition between research and development is made at the beginning of human testing (Phase I), probably delayed the full implementation of a cPoC type organization. By contrast, organizations such as Eli Lilly, which for many years included Phase I and Phase IIa in the research units, easily functioned as cPoC type organizations and are making the transition to sPoC organizations more rapidly. Another example is that of Novartis, in which the creation of the NIBR rapidly converted this organization from a cPoC to a sPoC focus. Finally, at Genzyme, the unique focus and the involvement of patients in the pursuit of drug innovation contributed to the company becoming one of the earliest adopters of a sPoC focus.

Of particular interest is the realization that the heads of R&D who embrace the sPoC model all seek to generate a bias for action that places the patient at the centre of the research effort. Navigation through the complexity of priorities in an increasingly large company is often the principal challenge.

Recommendations

Establishing and maintaining an entrepreneurial culture during drug development is perhaps easier than during the research stage as the activities associated with this later phase are closer to product realization and clinical application. The inherent sense of urgency associated with the development stage is driven by the competitive environment, in which time to market with a differentiated product is an important determinant of success. Thus, the creation of special product teams for individual efforts and for therapeutic franchises, which are co-led by development and commercial leaders, is more likely to foster the entrepreneurial behaviours we have identified, such as ownership, outcome focus, passion and conviction, and the ability to recruit the best people. During this stage, it is also easier to define successful outcomes, such as completion of a well-defined task in a rapid time frame, and so it is easier to create incentives that directly reward achieving these outcomes.

During the research stage, however, entrepreneurial behaviours are often compromised by several characteristics. These include:

- Increasing size and complexity of research groups
- Having large portfolios and a focus on increasing the number of 'shots on goal'
- Middle managers focused on timelines and portfolios, instead of science, technology and leveraging external knowledge
- Influence of the commercial department too early in the process
- The impact of evolving science and technology on organizational complexity
- A lack of alignment between Head of R&D and CEO with respect to the culture of research.

The responses from our interviewees with respect to these differences led us to the following recommendations:

- Organizational structures in research units should facilitate identifying the 'right drug for the right patient'. The rapid sharing

and integration of information generated by all the relevant disciplines, regardless of where it is found, must be assisted and rewarded. We recommend that companies seek to move towards the sPoC model (FIG. 1), which extends research to Phase IIa and also incorporates feedback from post-marketing surveillance studies to fuel the continued search for new targets, biomarkers and an understanding of off-target effects. These activities are crucial in the search for the right therapy for the right patient, and will heighten the sense of urgency to get drugs to patients.

- Middle managers should be given incentives to access the best ideas and the best people globally to drive curiosity and 'open innovation'. Managing external networks and rapidly internalizing the results of new scientific and technical approaches should also be among their priorities. Rewards for managers should be based on the speed with which they achieve the progression of projects, facilitated by their capacity to foster the integration of knowledge and to provide appropriate guidance to 'true believers' and 'mavericks'. Ultimately, companies should use middle managers to transform their culture from something analogous to a "supertanker" to "a flotilla of diverse, nimble and innovative ships", consisting of the following elements: focus on the patient, scientific curiosity, collaboration, speed to solution and rewards that are aligned with goals.
- Multidisciplinary research teams should consist of no more than 20–40 members who focus on the preclinical and clinical validation of novel targets/mechanisms with responsibility through to clinical proof-of-concept in Phase IIa trials. These 'units of innovation' should be supported by the traditional discovery research expert groups, such as molecular biology and chemistry, which focus on assessing the molecular validation or relevance of the target and finding lead molecules that interact with the target. Both of these groups should include specialists in post-marketing surveillance to ensure relevance to the patient. They should also perform relevant studies with academic clinicians to generate information from subsets of patients, which might inform the research efforts and ensure a sPoC approach.
- Heads of R&D must focus indefatigably on building and maintaining an appropriate entrepreneurial culture. Furthermore, the support of the CEO for this focus must be visible and active.
- Companies should be more innovative with respect to reward and recognition for discovery scientists, to foster bias for action, ownership and an appropriate sense of urgency.
- Companies should examine what we term the 'columns outside the doors' phenomenon and the subtle impact that this form of recognition might have on entrepreneurial behaviour. Smith described this phenomenon, which occurs across the world: as start-up companies become successful, they are relocated from humble laboratories to grander buildings with columns outside their doors. Interestingly, such edifices often violate the observed inverse square relationship between communication among scientists in laboratories and the distance between these laboratories. We offer this insight more as a provocative thought than as a firm recommendation.

We offer one final thought regarding the transferability of these insights from drug discovery research to drug development. In discovery, our data and previous research suggests that concept realization — the metric relevant for gauging the effectiveness of discovery — improves as the size of the innovation unit grows to around 20 to 40 researchers, but then declines as the size of the unit increases and diseconomies of scale take effect. In development, it is common wisdom that the optimal efficiency of the process is obtained when the size of the unit is considerably larger than the optimal size of discovery units. Interestingly, in large pharmaceutical companies, it has become increasingly common to outsource many development-related activities, and as this extends, it is likely that the efficiency–size relationship may be turned on its head, with pharmaceutical companies managing development with relatively smaller units than they have at present. In that case, the management of discovery units may hold valuable lessons for the conduct of development. These observations might stimulate large pharmaceutical companies to do that which Yamada maintains they can: "transform the industry."

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Competing interests statement
The authors declare competing financial interests: see web version for details.

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