

A perspective on scientific innovation in the pharmaceutical industry

With a tarnished reputation and a lack of sustainable innovation this article argues that, maybe, it is time for the pharmaceutical industry to look more closely at balancing the commercial needs of their organisations with the requirement to create the correct culture and environment for human innovation and creativity.

Over the course of the last decade, the pharmaceutical industry has developed a poor reputation with the public. Historically speaking, the work of biotechnology and pharmaceutical companies has brought the world numerous advances, such as penicillin and infant vaccinations. In the past 50 years, the industry has practically eliminated the occurrence of polio in the developed world and childhood leukaemia can now be cured in approximately 80 percent of cases¹. The industry should be known for its innovation, passion and contributions to humankind.

Instead, there is a lack of external appreciation for the cutting-edge work that is accomplished daily. Pharmaceutical companies are viewed by the majority of outsiders as financially greedy, providing high-priced new medicines that appear only marginally better than cheaper and seemingly as-effective generic products. Additional debates as to the ethical practices of the industry are further ignited by the price of prescription drugs and the rising cost of healthcare. While the lack of external appreciation for many important industry issues is concerning, it is particularly distressing for me personally when the public does not understand that the vast majority of the people involved in developing novel new medicines

do so for far more noble reasons than simple profit motives.

Of the scientists I know and with whom I work, those involved with the research and drug discovery phases of the pharmaceutical industry labour to craft new medicines as an act of faith, not an impersonal scientific endeavour. This perspective of industry researcher scientists is not ruled by monetary incentives or a yearning for fame, but rather a true and innate belief that

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someday all major human diseases will have a cure as a result of their collective dedication to laboratory research.

For those like me who are involved in the discovery of novel oncology molecules, the odds of success are very much against us. It is not uncommon for a pharmaceutical research scientist to spend his or her entire career working on molecules that never make it to human clinical trials, much less receive US Food and Drug Administration (FDA) approval for use by patients. Even if a new oncology compound enters clinical trials, the chances of that compound being launched commercially hover around 5%². The odds in other therapeutic areas are only marginally higher.

Based on these odds of 'success', one might classify these researchers, or drug hunters, of the pharmaceutical industry as either the largest assembly of fools on the face of the Earth, or perhaps, the largest congregation of optimists in the galaxy. Given my career choice over the past 30 years, I vote for the latter and I hope you do as well. If you judge people by the challenge they are willing to accept – while fully understanding the probability of failure – then I would view my courageous colleagues in drug discovery with the highest of esteem.

As Chief Scientific Officer at Millennium: The Takeda Oncology Company, I have the great honour of working with a group of highly talented people who I believe are among the world's most dedicated drug hunters. The scientists I work with every day at Millennium share a mission with those from across the industry: to invent new medicines

for people with life threatening and debilitating diseases. We share the goal of bringing innovation to fight disease, but this goal is often thwarted by other factors.

The problem of innovation

Periodically, groups of industry scientists and executives get together at various professional meetings to share their research experiences, discuss industry trends, and collectively argue about the future of drug research and development. Among the range of topics for discussion afterward is one that ubiquitously garners much emotion and analysis. It is a simple, yet seeming multifarious question: "What happened to innovation in the pharmaceutical industry?"

Almost everyone attending these conferences has something to say about how we may have veered off the path of innovation. Pharmaceutical consultants in particular have made their careers by analysing, designing and strategically implementing a myriad of solutions aimed at pulling the pharmaceutical industry out of its innovative doldrums and on to the course for innovative recovery.

I believe that all of participants in these discussions, including consultants, scientists and administrators, bring unique and important perspectives to this important debate. There are undoubtedly many ways to address the challenge of innovation, and one solution will not fit every organisation's needs.

Business imperatives and scientific innovation

Numerous contributing factors impact any pharmaceutical company's success or failure to discover innovative medicines in a sustainable manner. My perspective is the collective impact on an individual company's discovery governance, structure and most importantly culture creates the most dominant negative long-term consequences. And although they can be categorised as independent entities, these negative innovation-suppressing factors stem from two common sources: (1) commercial drivers operating within a context of short-term business growth expectation cycles and (2) the high investment required to bring new molecular entities to the marketplace. Given the very long time lines – a key component of overall cost – required to discover, develop and commercialise an average drug (see below), conflicts between business needs and research needs seem unavoidable.

Commercial considerations and business cycle-based imperatives are part of the world in which

all businesses operate. In the pharmaceutical industry there is great value in having research organisations understand the realities of the marketplace just as understanding the pathophysiology of disease significantly enhances decision-making in all facets of drug discovery and development. However, when commercial opportunity alone represents the dominant lens through which research and drug discovery is directed, the environment for scientific innovation and breakthrough therapeutics is diminished.

The investment required by the pharmaceutical industry to bring a new medicine from discovery through development and eventual commercialisation exceeds \$1.2 billion and takes an average of 12-15 years³. This reality unfortunately necessitates that the cost of new prescription drugs to the consumer can be significant. What is most often overlooked externally is that the eventual price of a marketed drug must incorporate the cost of the all those molecular entities that never make it to commercialisation. Only 8% of oncology drugs that enter into clinical trials are eventually approved for use in patients³, leaving the preclinical and clinical costs of those cancelled drugs to be absorbed by the sponsor company. The initial approval for an oncology drug provides market entry (usually in the third or fourth lines of treatment) but requires enormous continued investment in order to reach all of the potential patient groups (designated by cancer type and sequential therapeutic disease progression strategies) that might benefit from the new drug. It is equally important to understand that regulatory approval to market a new molecular entity does not by any means guarantee that the company sponsor will ever return a profit on this product. In the increasingly segmented oncology market place, it is not unusual that only the first two product entrants into a modality and disease segment reach commercial expectations. It is thereby understandable that investment reduction strategies (such as distribution of various discovery functions to different geographic regions with lower FTE and operating costs) as well as drug target and indication probability of success risk reduction strategies (the usual genesis of 'me-too' drugs) have been widely implemented by the pharmaceutical industry.

Once a new molecular entity is launched – irrespective of therapeutic area – the drug likely has only a few years of market exclusivity before the 'me-too' compounds begin to receive marketing approval. Follow-on competitor compounds normally do not have to prove themselves to be clinically superior to the original (although this does

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happen). Rather, the ‘me-too’ is more commonly required to demonstrate non-inferiority in safety and efficacy. Additionally, the introduction of these follow-on drugs normally does not lead to a lower overall cost of the particular drug class. It is likely, however, that expenditures associated with marketing and sales of both the novel and follow-on compounds will increase around this time and continue on to be an increasing expense for years to come.

Creating a me-too drug certainly increases the chances of financial success for a company through decreasing the risk that the drug target and indication will not be validated in clinical trials. This can be likened to Hollywood producers making a steady income from remakes of older films, regardless of whether the original film was financially successful. Hollywood often receives criticism for its lack of creativity and commercial greediness displayed by creating remakes. The pharmaceutical industry suffers from the same fate when many follow-on drugs are brought to market for the same medical need. This model makes great commercial sense (for either the film or drug industries), but positions our industry for significant, often unfavourable, external scrutiny from patients and the media as well as public and private institutions that pay for the largest portion of these new drugs.

Understanding and investing in innovation

I believe over the past 20 years the pharmaceutical industry has ignored what it really takes to invent

innovative new medicines. As an industry we did not invest appropriately in understanding the factors that shape an innovative discovery culture and in the process marginalised the creative human element.

For whatever combination of reasons – all seemingly informed and perfectly logical at the time, a view emerged over that last decade or two that innovative drug discovery was fundamentally an engineering problem. To address this problem the pharmaceutical industry invested heavily in dazzling technologies, cool instruments, informatics and computational platforms of all types, every conceivable new twist in synthetic organic chemistry and, of course, genomics and all the other combined ‘omics’. What has emerged from this era is the globalisation of pharmaceutical drug discovery process that incorporates a scalable series of technologies distributed by scientific discipline and often geographically dispersed (to lower cost or as a result of the last round of merger and acquisition); all orchestrated at the top by a strict set of guidelines and metrics that – at the end of the day – should produce a continuous flow of compounds into the clinic. A numbers game if you will such that the yearly discovery output – the so called ‘shots on goal’ – will rise above the number of ‘assets’ needed to statistically yield new medicines. Almost everything about the industrialisation and globalisation of drug discovery makes sense except for the fact that it has failed to deliver the expected innovative product flow. Drug discovery organisations are often described as impersonal ‘discovery engines’. This mechanised assembly line mentality may be a very fine way to build a car but I would argue a rather poor way to attempt the crafting of a potential new medicine.

I believe the achievement of sustainable innovation stems from making a committed investment in understanding the motivation that drives the people of an organisation to persevere together through adversity. Making new medicines is the goal of drug discovery organisations and represents an achievement of such magnitude that inspires and unites individuals to strive towards this objective. Making new medicines is also the most complex team sport on Earth. The discovery process involves a group of biologists of all persuasions – engineers, physicians, chemists, physicists, mathematicians, physiologists, pharmacologists and statisticians (to name a few) – all coming together and practising their craft as an effective, integrated team with a common goal to engage in multi-dimensional problem-solving in real time.

It is critical that drug discovery scientists be

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References

- 1 American Cancer Society. What are the key statistics of childhood leukemia? 14 May 2009.
- 2 Wintergreen Research Laboratories. Oncology market opportunities, strategies, and forecasts: 2006 to 2012. Wintergreen Research Laboratories, 2006.
- 3 American Enterprise Institute for Public Policy Research. Oncology drug development: rethinking FDA oversight. 14 March 2008.

closely associated with therapeutic area focused collaborators in clinical, regulatory and drug safety organisations in order to practise continuous drug target to clinic strategic and operational alignment. Inclusion of discovery scientists throughout the development process is necessary to enhance communication and provides an essential cultural framework that acknowledges those key primary motivating principals so meaningful to those who created the clinical candidate.

Measuring and rewarding innovative successes

The earliest indication of potential success for a new molecular entity in most cases is the clinical proof of concept. If having a clinical proof of concept is the first meaningful milestone, then the timeline between compound invention and this clinical milestone is incompatible with typical measures of individual career progress. As an industry, we must decide upon other, more meaningful and timely ways to set incremental goals and reward the smaller successes and individual contributions associated with team problem solving that is fundamental to innovation. What is it then that is important for team success, reward and recognition? How do we reconcile the individual need for recognition within a team environment, knowing there is an overarching organisational business requirement for the team to produce an innovative product with prescribed regularity?

I believe one answer to these complex and seemingly intractable issues lies within management's investing in an intimate understanding of the contributions made by individuals within a team. It is important for management to have an understanding of each individual's knowledge of problems confronting the team as they arise, and having an appreciation of what an outcome really means. Management must be capable of distinguishing excellence from average performance, and average from poor; the consequences for not committing time and energy to this investment are significant – a lack of innovation. If poor performers cannot be distinguished from those individuals and teams striving to be the best, the best and brightest will soon lose the pride, enthusiasm and energy needed to persevere through the quagmire that is drug discovery. No organisation can survive without inspired people who are willing and driven to sustain an innovative culture. Measures must be put into place that reward the individual, and at times the team, for well-executed innovation. Without those inspired people the organisation cannot sustain an innovative culture and will succumb to a

quantity over quality model, which brings us right back to where we started.

Moving forward

So the question remains, what is it that becomes the most important element required for developing and sustaining innovation in drug discovery? It appears clear, at least to this scientist, that assembling smart, knowledgeable, dedicated scientists armed with the latest and greatest technologies is not enough to ensure innovative success in the pharmaceutical industry.

I believe that the single, most important underlying factor governing the success or failure of drug discovery innovation is the culture within the discovery organisation of a company. Success in crafting new drugs is about creating the correct culture for human innovation and allowing creativity to take over at the appropriate time. These scientists must also be nurtured to be innovative assets to the company and recognised when they come through. In my view, it is a fundamental responsibility of our industry's executive management to dedicate time creating and maintaining a culture of innovation and recognise that it must be meaningful at the level of the individual discovery scientist. Otherwise, the lack of true scientific progress and thereby the discovery of innovative new medicines will continue to be our industry's fundamental problem. DDW

Dr Joseph Bolen joined Millennium in 1999 as Vice-President of Oncology. Since then he has assumed roles of increasing responsibility, and was appointed Chief Scientific Officer in 2006. In this role, he heads all biological research for the Company. Dr Bolen earned bachelor's degrees in Microbiology and Chemistry and a PhD in Immunology from the University of Nebraska.