editorial

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The road ahead for large pharma: long-term science and innovation

The road ahead for large pharma is increasingly challenging. For many years, the obstacles we face have continued to grow and critics declare our industry's prospects to be dim. The authors of this editorial take a more optimistic view: namely that those with a long-term vision to exploit the intellectual assets internally and externally, who focus in disease areas of genuine unmet need – using the right science and technologies, developing the right products, for the right patients, at the right differentiation and value – will prevail. These innovators will open new paths and make their way successfully, if not always smoothly, as they carry on with their journey to address eternal global medical needs.

For many years, large pharma R&D has delivered products with major medical benefits for patients [1]. There is no denying, however, that the pressures facing large pharma are coming from all sides. Many major drugs are facing patent expiry, potentially reducing funds for future investment into R&D. In some disease areas (such as hypertension), the number of good medicines already in the market is shrinking the window of opportunity for new discoveries, thereby diverting new research into areas of increasingly complex science. Even with all the promise of groundbreaking advances in science and medicine, current pharma productivity lags, as demonstrated by the low numbers of new molecular entities approved by regulators in recent years.

One reason for this is that regulators themselves are setting the bar higher, requiring additional data with more-extensive proof of safety and efficacy. Even after a new drug has cleared all hurdles for approval, pricing remains a crucial and constant issue as payers seek to limit reimbursements and access, unless differentiation is perceived to be sufficient. A fair price is important to provide the flow of funds for continued R&D.

By contrast, the ongoing science and technology revolution in the biomedical arena continues to enable drug discovery by increasing our understanding of disease pathophysiology and patient stratification of disease, enhancing drugable space for small synthetic molecules, adding new therapeutic modalities such as monoclonal antibodies and allowing the applications of predictive drug discovery to remove or minimize side effects, as well as refining DMPK and formulation issues (Table 1).

At the same time, there are many factors driving the needs for new beneficial medications including the rise of emerging markets, aging demographics, better disease detection and 'theragnostics'. New diseases are emerging including 'diabesity' in the younger population, antibiotic resistant bacteria and viral

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TABLE 1

Drug-hunting science

	Advances	Obstacles
Disease understanding	Human genome/proteome/ disease pathway mapping	Multiple disease causes, mechanisms vs safety
Therapeutic agent—generation	Expanded chemical space Biologicals Emerging agents, for example, siRNA	Non-drugable targets Cellular penetration
Therapeutic agent—optimization	Frontloading of DMPK, safety, formulation Humanized models	Substance properties, Synthesis routes Relevant animal models
Clinical testing	Mechanistic exploitation cross diseases including combinations Biomarkers Patient selection, study design Translational models in man	Translation of animal data to patients Clinical efficacy/safety Drug–drug interactions Patient variability Regulatory and payor hurdles—differentiation

infections. Furthermore, comorbidities of diseases are increasingly common.

Mergers and acquisitions (M&As) are becoming traditional ways to increase market share and add new capabilities, technologies, therapeutic areas or pipeline candidates [2,3]. But M&As require diligent leadership because they can also shift focus away from project delivery and create unrest and demotivation because of associated reorganizations and downsizing. M&A lies at one end of the range of externalization strategies. Along the way are a whole host of research collaborations, partnerships and investments aimed at identifying and developing more new ideas and technologies at ever earlier stages.

Looking inside, companies are implementing programs to improve productivity. This must be aligned with a deeply rooted and sustained focus on performance within a long-term strategic context. One widespread approach to working more efficiently and effectively is Lean Sigma, which combines Lean Thinking (eliminating non-value-adding steps) and Six Sigma (reducing variation in processes). At AstraZeneca, we have been embedding Lean Sigma across our drug discovery and development processes, working with each department to support the value chain and develop a culture of continuous improvement within an innovative research environment. The staff embraced this new thinking and major improvements have been made rapidly, cutting certain lead times in half in the design-make-test compound cycle. To save costs, non-core activities have increasingly been outsourced to low-cost providers and our management skills of external activities have been boosted.

Project failures represent a waste of important intellectual assets and mechanisms must be in place to avoid repetition of mistakes. We have learned from our experiences and have since been implementing strategies to spark innovation based on high-quality science and technology, while improving the speed of delivery and reducing cost. Among the components we have relied on are deep disease area expertise, lead generation, frontloading of safety and DMPK early in the value chain, translational science, biomarkers, predictive science and information exploitation, externalization and biopharmaceuticals expansion.

We also prioritized our disease areas on the basis of unmet medical need, access to breaking science, discoverability, developability, competitive edge and commercial attractiveness. Included in the activities are also efforts on neglected diseases such as tuberculosis. Target product profiles (TPPs) are shaped by patient and payor insight and disease mechanisms are aligned to those TPPs. Selected molecular targets are approached with multiple candidate drugs (CDs) to offset the risk of project/class attrition and to provide both back up and follow up CDs for 'must win' projects. Furthermore, within discovery we have developed an empowered organizational model, with each disease area owning its own strategy, resources and accountability to deliver CDs. These areas have critical mass and strong project delivery teams that share best practice and work closely and cross-functionally with safety assessment, enabling and platform technologies, informatics and various development functions. As a result, our CD output from discovery into preclinical development and human testing has increased threefold since 2000, in spite of more demanding internal stage-gate criteria, which have been externally recognized as the best early-stage pipeline in the industry by R&D Directions for three years in a row [4]. Several of these compounds are now in late phase pivotal trials.

Going forward, we are determined to increase our success rate during development by providing better choice for Phase III starts. This has always been a long, costly and risky endeavor for our entire industry. It is now estimated that it takes more than US$ 1 billion and a dozen years to bring a single drug (either small molecule or biological) from concept to commercialization—and the majority fail [5,6].

Increasing industry success rates and delivering more medicines is challenging, but by no means impossible, especially with the more predictive scientific tools now available. We stand at a very exciting phase in our industry (Table 1). Science and technology have never been so promising nor have delivered so many opportunities to improve health and extend lives, but continued investments are needed in both the public and private sector, in spite of the current economic climate. Therefore, we welcome and participate in public–private partnerships, such as the Critical Path Initiative in the USA and the Innovative Medicines Initiative (IMI) in the EU.

All big pharmas have to counter the challenge of patent expirations of major products and, at AstraZeneca, we believe our success will be bolstered by having a competitive and risk-balanced portfolio of projects, both on small and large molecules, which derives from internal programs or from collaborations with external partners. We believe that, in future, preventive and curative treatments will be more common and that diversity between individuals and within populations will be further recognized

TABLE 2

Big Pharma R&D

Opportunities	Pitfalls
Strong drug-hunting expertise. Accessing best scientists internally and externally **Genuine willingness to consult and learn from collective memory**	Bureaucracy; process oriented static culture; poor corporate reputation
Broad technology platforms	Lack of focus with frequent strategic shifts
Value chain integration (Discovery, Development, Production, Market)	Unwillingness to change; 'silo mentality'
Global asset and knowledge exploitation, learning from failures	'Not-invented-here' syndrome
Small unit feel (empowerment) within large global organization (power)	R&D funding mainly late stage and short term
External transparent mindset	
Intelligent risk taking, broad portfolio	'Me too' approach
Long-term innovation with constant improvements. Clear, sustained goals	Constant reorganizations and mergers—demotivation

and understood. We have formed a special Personalized Healthcare team to help us in addressing the challenge of personalized medicine, and biomarkers are now used routinely throughout early development. This is all part of how we are working to deliver the right products to the right patients, at the right doses and at the right time.

We rely increasingly on validated predictive tools for preclinical, clinical proof-of-mechanism and proof-of-concept studies that, together, help to promote better efficacy and safety. In all we do, continuous improvement is key, especially when it comes to harnessing the collective knowledge that exists within the large organization about our projects. Here is where we can provide more of the right kind of differentiation and value to patients and payers and exploit common mechanisms and pathways across disease indications as well as for new opportunities outside our traditional disease areas.

A summary of opportunities and pitfalls for big pharma R&D is given in Table 2.

The most important factor in all we do is our people. They are the drug hunters, the champion innovators and our competitive edge—being scientifically cutting edge and on par with external partners, which is the reason we remain optimistic for the future of our company despite all the challenges we face. In them, we see a genuine passion for science that, in our best scientists, only intensifies over an entire research career. We recognize and celebrate our innovators and invite them to help direct our strategies, train others and share their success stories. We must continue to nurture their talents by providing them with an information-rich environment, where internal science is shared and external collaborations are encouraged. Science is not perfect in drug discovery and development, but history tells us that most successful drugs have had issues to overcome: winners in future will have the people that can solve complex problems and use intelligent risk taking, often with the help of external partners. While we have put appropriate reward systems in place to address both short-term and long-term delivery achievements, we must not overlook the importance of the satisfaction that comes from engaging in exciting science, in the company of intellectually stimulating colleagues, without which no reward scheme can motivate staff for long. Finally, the ultimate reward is to transform science into meaningful medicines that help patients live longer and healthier lives.

References

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5 These statistics come from John Patterson's ''Viewpoint'' in *Pharmaceutical Technology Magazine*, ''Can Big Pharma Produce the Next Generation of Medicines?'', August 2, 2008

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