

What are the obstacles to innovation in the pharmaceutical industry?

Innovation is a key word throughout the pharmaceutical industry and the healthcare community¹ and its pursuit is a business imperative for Pharma.

Pharma urgently needs to produce innovative new therapies if it is to overcome its critical, long-term challenge, ie the revenue gap produced by the industry's failure to develop sufficient, new, patent-protected medical therapies to offset the revenues lost as existing products lose their patent protection (Figure 1)².

Contributing to this challenge is a relentless downward pricing pressure. "Indeed," reports Steven M Paul et al³, "for every dollar lost in declining product revenues due to patent expirations by 2012, it has been estimated that large-cap pharmaceutical companies will only be able to replace on average 26 cents with new product revenues."

The pharmaceutical industry's responses to this pressure are multi-faceted. Some companies have increased expenditure on R&D (see Figure 2), others have engaged in enhanced merger and acquisition, many have reinforced their product in-licensing capabilities, all seem to be reorganising and only a few have not instituted considerable staff cutbacks. In 2009 the industry lost >60,000 jobs and in 2010 >50,000⁴. To produce the next generation of innovative medical therapies, pharma urgently needs better, faster and cheaper drug discovery and development processes. However, none of these business adjustments has resulted in significant progress to date.

What is keeping pharma from innovating? Cynics might argue that the barriers lie in the processes of R&D itself and the relationships between scientists and their supporting corporate functions such as information technology, intellectual property, legal, procurement and quality assurance. However, what-

ever the counter-innovative influences of these functions might or might not be, the fundamental obstacles to innovation more accurately reside in the industry's inability to enable intra- and inter-company organisations to exchange information securely and in an unequivocal and understandable way. Innovation is blocked by the industry's reluctance to let go of unnecessarily individualistic business processes utilising ill-defined, non-existent or poorly accepted data and information standards.

Pre-competitive collaboration

Precompetitive collaboration enables all pharmaceutical industry stakeholders – lifescience organisations, technology vendors, publishers and academics – to work together in order to codify best practices, signpost ways of working and develop standards that can spur innovation. This paper provides some insights, gleaned from the Pistoia Alliance community, into what is impeding innovation in pharma and provides examples of how precompetitive collaboration can identify common use cases and from them, derive appropriate and useful information standards that improve the interoperability of R&D business processes.

Identifying barriers to innovation

Many commentators have identified barriers to innovation in pharma, including Warren Kaplan, who compiled the following list in 2004⁵:

- Inadequate understanding of basic science for certain diseases and the identification of targets amenable to manipulation.

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- Figure 1**
- Regulatory authority ‘rituals’ with regard to preclinical and clinical testing procedures that may, or may not, have basis in empirical evidence.
 - Differences in perception of risk among different stakeholders.
 - Uncertainty about the timing and level of reimbursement decisions leading to uncertainty among stakeholders.
 - General business uncertainties in drug development.
 - Potential increases in the cost of doing business due to intellectual property concerns.

Regulatory agencies have also taken on a key role in advising pharma on how best to solve its innovation challenges – an interesting development given that regulators are ultimately responsible for the approval (or lack thereof) of marketing authorisation for new medical therapies. The FDA published its report ‘Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products’⁶ (more commonly known as the Critical Path Initiative) in March 2004. Not to be outdone, ‘The European Medicines Agency Road Map to 2010 – Preparing the Ground for the Future’ was published by the EMEA at the same time with the promise to “help to stimulate innovation, research and development in the European Union (EU)”. The World Health Organisation also entered this advisory vogue with its ‘Priority Medicines for Europe and the World’⁷ which references “innovation” and “barriers to innovation” a multiplicity of times. Also in 2004, EFPIA and the

EU created the Innovative Medicines Initiative, to which the European Commission’s Seventh Framework Programme will contribute €1 billion and member companies of the EFPIA will provide at least another €1 billion in matching, in-kind contributions⁸. The IMI’s Strategic Research Agenda⁹ states in section 1.5: “It is important to appreciate that IMI will not – and is not expected to – deliver new medicines *per se*. However, it is expected to deliver powerful new multi-disciplinary tools to improve the innovation process and thus establish a new drug development paradigm.” One of these tools is knowledge management and indeed all these above referenced seminal texts point to the importance of IT or knowledge management in the delivery of these innovation initiatives.

The Pistoia Alliance (<http://www.pistoiaalliance.org>) originated in this rapidly developing, pharmaceutical industry-wide imperative to enable and enhance innovation. During a meeting in Pistoia, Italy in 2007, a group of senior pharmaceutical industry R&D IT directors concluded that many of the activities carried out by researchers in bioscience organisations were remarkably similar. For example, the activities to determine a gene sequence, identify a signal transduction pathway, search a chemical repository or keep abreast of the scientific literature were all of course necessary, but remarkably common. They identified that much replication of effort by their respective R&D IT organisations might be minimised if they shared thinking about, defined and then documented the best practices for these precompetitive research activities. This would enable expert, third-party organisations to build and deliver such services to many companies. The money saved by sharing the costs of provision of precompetitive scientific services could be redeployed for company-specific, strategic, transformational, innovative initiatives.

Precompetitive alliances such as the Pistoia Alliance expose a disconnect in the industry between the pursuit of innovation and actually achieving it. Recent conversations on the Pistoia Alliance website (<http://www.pistoiaalliance.org/blog/2011/05/whats-strangling-pharma-innovation>) and at the Pistoia Alliance’s inaugural conference in Boston, MA, in April 2011 reveal several opinions from technology vendors, academics and consultants about what is hindering innovation.

Richard Resnick, CEO of GenomeQuest, places the blame on:

- Top-down corporate strategies that fail to recognise the innovation happening at the lower levels of the company.

- A systemic desire by informaticians to build precompetitive tools on their own, rather than investing their effort in developing tools that will provide competitive advantage.
- An enterprise-wide culture of letting 'perfect' get in the way of 'good enough'.
- An inability to understand the fully-loaded costs of research.
- An inability to measure the ROI of partnerships and customer-vendor relationships.
- A lack of empowerment of innovative departments with sufficient budget to be nimble, even if it means duplication of effort across the enterprise.

Hedley Rees, a consultant and author with expertise in the pharmaceutical industry supply chain, noted that in his experience, "senior management boards still believe drug discovery and development is about a 'lucky strike' followed by a race to the clinic to get an approval; anything else is off their radar screen". They do not afford sufficient time in the critical early stages of drug development to 'stress-test' the robustness of their compounds destined for market. The net result is that only one in 250 survives the journey from development candidate to regulatory approval¹⁰.

If that is the case, one could conclude that several key elements are 'off the radar screen' of senior management. Work in the research laboratory, for one. As Niggi Graber, a lab automation specialist in Pharma, observed: "Innovation happens in research labs and is heavily dependent on the availability of appropriate IT support as well as on a flexible use of equipment in the lab. Legacy data architecture and IT structures are major obstacles in providing required information across the company. On the other side rearrangement, replacement of existing equipment and an easy and rapid adoption of new equipment based on new technologies have to be realised faster and faster. It is the aim of SiLA¹¹ to remedy this situation by establishing globally, provider-independent, open standards for device integration and for data interfacing. This enables pharma and biotech R&D to focus on its main business by reducing equipment connectivity efforts to a minimum.

Also 'off the senior management radar screen' is ambitious and effective management of IT in pharma. As another correspondent remarked: "Consider the general case of IT organisations in pharma. IT reports into the CIO who, in turn, reports into the CFO and CFOs tend to regard IT as an expense rather than an urgently needed opportunity. And that brings us to the question of why pharma CIOs seem to understand little of the

end-to-end information flows in the companies they serve. Rather they focus on attempting to drive out cost, running internet auctions for several thousand desktop computers or struggling with implementing SAP. None of which contributes in any way to innovation."

Another respondent complained about trying to use technology innovatively in the regulated domains of the industry. "QA departments which regarded themselves – not the business owners – to be the arbiters as to whether or not a validated system could be released into production – and the QA departments which agonise over Computer Systems Validation templates or demanding thousands of pages of documentation to be produced (that no-one will ever read again) when validating a common, best-of-breed, off-the-shelf-commercial product. And then the QA departments which still struggle to implement a risk-based validation methodology to include the opportunity of pharma using cloud-based services."

Other contributors were frustrated by the replication of research activities in pre-competitive areas. Such unimaginative effort, said one, "sounds like a serious waste of money"!

Smart innovation: going far by going together

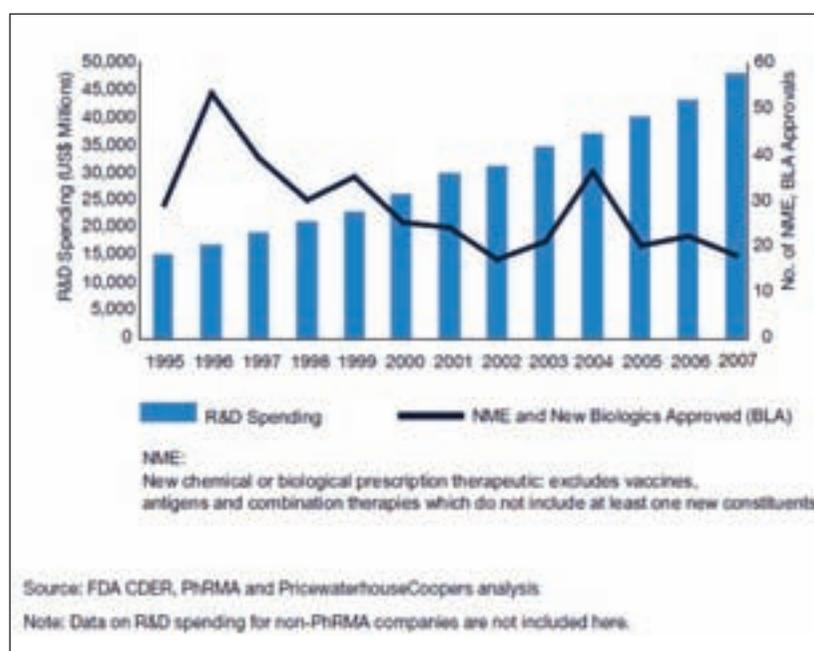
What does this admittedly small sample of responses indicate about barriers to innovation in the pharmaceutical industry? There seems to be only a little concern about a fundamental shortage of resources for R&D. However, there is concern

Further reading

Williams, Michael. Productivity Shortfalls in Drug Discovery: Contributions from the Preclinical Sciences? *Journal of Pharmacology and Experimental Therapeutics*, Vol. 336, No. 1. (1 January 2011), pp. 3-8.

Grasela, TH, Slusser, R. Improving Productivity With Model-Based Drug Development: An Enterprise Perspective. *Clinical Pharmacology & Therapeutics*, Vol. 88, No. 2. (30 June 2010), pp. 263-268.

Figure 2



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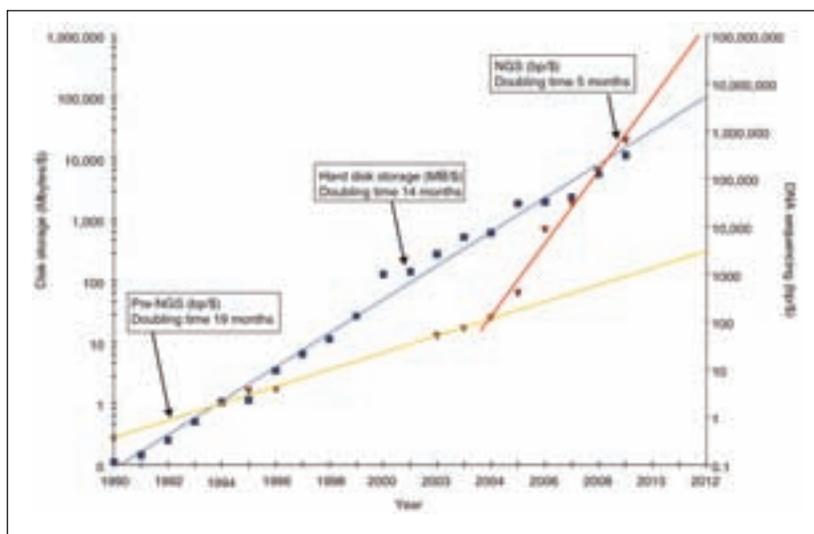


Figure 3

Historical trends in storage prices versus DNA sequencing costs. The blue squares describe the historic cost of disk prices in megabytes per US dollar. The long-term trend (blue line, which is a straight line here because the plot is logarithmic) shows exponential growth in storage per dollar with a doubling time of roughly 1.5 years. The cost of DNA sequencing, expressed in base pairs per dollar, is shown by the red triangles. It follows an exponential curve (yellow line) with a doubling time slightly slower than disk storage until 2004, when next generation sequencing (NGS) causes an inflection in the curve to a doubling time of less than six months (red line).

These curves are not corrected for inflation or for the 'fully loaded' cost of sequencing and disk storage, which would include personnel costs, depreciation and overhead. Stein. *Genome Biology* 2010 11:207 doi:10.1186/gb-2010-11-5-207

that those resources are not optimally deployed – indeed are wasted – by R&D organisations. This is caused by companies replicating precompetitive activities rather than pooling their resources to achieve common, shared objectives. Other commentary focused on research processes and their information flows not being 'joined up'. Furthermore, those processes that occur in the regulated domains of the industry – and hence are subject to validation – come under scrutiny. Are the approaches to validation in general, and computer systems validation in particular, fit-for-purpose in today's sophisticated technology age? Validation practices could be considered obsolete, very time-consuming, very expensive and as such discouraged adoption of newer and more agile, 'innovative', computer systems, such as cloud-based SaaS solutions. Our respondents were frustrated with pharmaceutical industry senior management being captivated by the allure of serendipity or the 'lucky strike'. Senior management seemed unwilling or unable to get to grips with some of the fundamentals of R&D operations that so urgently need to be re-engineered to enable, rather than hinder, the innovative work of the R&D scientists.

These challenges are tractable; none is insurmountable. If senior management in pharma R&D were to engage in R&D operational excellence, companies could make rapid progress in overcoming these barriers to innovation. One ready-made approach would be for them to directly invest in, and provide active and engaged support for, the work of organisations such as the Pistoia Alliance. For it is these not-for-profit, cross-company organisations that are ideally positioned to establish

opinion-forming working parties of industry-respected practitioners to think through and find widely-accepted solutions to resolve issues that inhibit innovation.

Part of the *modus operandi* of the Pistoia Alliance is to encourage the cross-company conversations that identify the most pernicious examples of resource-wasting replication of pre-competitive research activities – and then to launch project teams to address these challenges. At its founding in 2009, The Pistoia Alliance set out a programme of work around the following technology pilots:

- **Sequence Services:** Defining and documenting an externally hosted service where organisations can securely store and mine both in-house derived gene/sequence information as well as the public domain gene databases.
- **SESL (Scientifically Enriched Scientific Literature):** Exploring the feasibility of an Amazon.com-like 'brokering service' that scientists can use rapidly to gather information on disease-causing genes.
- **Electronic Lab Notebook (ELN):** Defining a common standard that would enable scientists to use the same query across any and multiple ELNs.
- **VSI (Vocabulary Standards Initiative):** Defining and publishing a standard, vocabulary-based methodology for querying the scientific literature and bioinformatics databases such that all hits are found against molecular drug target search criteria rather than a subset.

The Sequence Services Project exemplifies how precompetitive collaboration can produce useful solutions. Life science R&D needs access to both public and proprietary gene sequence data. Historically, each lifescience R&D function has taken a copy of the public domain data and mounted it safely behind the company firewall. In this self-evident security, scientists have used similar or the same software tools to compare and contrast their corporate-specific gene sequence data with public domain data in order to make scientific decisions. But times have changed. The technology of gene sequencing has become so advanced that the production, quantity and availability of gene sequence data is outstripping Moore's Law's ability to accommodate it (Figure 3)¹². As the Red Queen told Alice: "It takes all the running you can do, to keep in the same place"¹³.

Phase 1 of the Sequence Services project brought together bioinformaticians from several pharma companies under the aegis of the Pistoia Alliance to

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formulate the business, scientific and functional requirements for a common, shared, externally-hosted sequence service. Performance, availability and security capabilities were all considered. Four technology vendor companies or consortia were then selected to build functional and testable sequence service installations¹⁴: Constellation Technologies and Microsoft, Eagle Genomics and Cognizant, Infosys and Thomson Reuters. The working group then checked the security robustness of these systems through an independent 'ethical hack' carried out by AT&T. The resulting proofs of concept are publicly available from the vendors for evaluation.

Phase 2 of the project will supplement these already demonstrable businesses and scientific capabilities with an enhanced, cross-company, commonly-defined scientific toolkit including open source codes as well as workflow. These requirements will be published as an RFP in mid-2011 and the vendor community will have the opportunity to display its technical and business prowess in meeting these requirements cost-effectively and securely.

The benefits of such precompetitive work are clear to all the stakeholders. The larger lifescience R&D companies are looking to reduce their cost of sequence services by at least 50% thereby liberating resources for innovative, transformational projects. Some of the smaller lifescience R&D companies – who so far have been unable to afford the technology to perform these sequence services – envisage a future where they too will have access to this fundamental, non-discretionary, scientific toolkit through the cloud. The Sequence Service providers see the opportunity to generate revenue.

Conclusion

The pharmaceutical industry certainly pays lip service to 'innovation', but is it really committed to achieving it? What is evident is that there is no clear strategy of how innovation should be encouraged. At a high level, innovation is undoubtedly a complex function of patients' needs, providers' capabilities, appropriate funding, regulatory frameworks, incentive mechanisms and intellectual property rights. Nearer the research bench, though, innovation may have more to do with senior management getting actively engaged in some of the detail of R&D operations. How does the CIO think he is supporting R&D? What are the reasons why legal will not let R&D information be stored in the cloud – and can those reasons be addressed? Pharma in general and pharma R&D in particular is a high-risk business in dire need of

innovation; critical service functions, eg IT, legal, procurement and QA should partner with R&D to understand this need and cut through red tape to create a true innovation culture.

The Pistoia Alliance is firmly committed to supporting R&D at the research bench. Its project teams identify common use cases, establish best practices, define user requirements, create proof-of-concept implementations, signpost standards, and offer thought-leading perspectives on how pre-competitive collaboration can lower barriers to innovation. Our members are committed to encouraging expert, external, systems suppliers to provide hosted, secure, shared resources to support R&D processes in the precompetitive domains of the life science R&D industries.

The Pistoia Alliance is particularly keen to receive readers' ideas about innovation and the barriers to innovation; please leave comments on our blog: (<http://www.pistoiaalliance.org/blog/2011/05/whats-strangling-pharma-innovation>)

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The Pistoia Alliance was established as a members' organisation in 2009. Today, it includes more than 45 member organisations encompassing life science companies, academic groups, informatics vendors and publishers. Together, Pistoia Alliance members aim to lower barriers to innovation by improving the interoperability of R&D business processes through precompetitive collaboration. The organisation focuses on bringing stakeholders to the table to define common, conceptual steps of the life science R&D workflow.