

AN AUDIENCE WITH...

Steven Paul



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What are the main factors affecting the biopharmaceutical industry these days?

Two of the most critical factors are declining R&D productivity and the large number of upcoming patent expirations. In 2007, just 19 new molecular entities (NMEs) were approved by the FDA, the lowest number since 1983, when the industry invested less than 10% of our current investment in R&D (over US\$50 billion per year). This low number of approved NMEs is compounded by the revenues that will be lost with the next large round of patent expirations. Reportedly, by 2015 or so \$200 billion worth of branded medicines will lose patent protection. All of this has put enormous pressure on R&D organizations, like ours, to replace pipelines every 10 years or so with a large number of even better medicines.

How have these environmental factors influenced Lilly's approach to R&D?

At Lilly, virtually every molecule we are pursuing is directed at what we refer to as an 'unprecedented target', whereby the mechanism of action for that potential medicine has not yet been unequivocally established to produce a desirable clinical benefit. This strategy of course increases the development risks but also potentially the reward, as these medicines could change the standard of care for a given disease and hopefully will replace older, less effective medicines. To do this affordably, however, we have deconvoluted the entire R&D process and reconstructed it by implementing a number of new approaches to improve productivity. For example, first we must choose better drug targets, including proteins or pathways informed by human genetics and genomics. Second, as late-stage attrition — often due to lack of efficacy — is one of the key reasons for declining R&D productivity, we establish clinical proof of concept (POC) as early as possible, preferably before Phase II, using surrogate end points,

biomarkers and even clinical end points. We do this for most of our drug candidates. For some medicines and diseases we cannot use clinical end points to establish POC. For two of our late-stage Alzheimer's disease (AD) therapies (a γ -secretase inhibitor and an anti-amyloid antibody) we have used various amyloid biomarkers to show that these medicines are having the desired effect on the drug target — either reducing brain production or enhancing clearance of the amyloid A β peptide. Hopefully, these approaches, when applied broadly to the majority of compounds in our pipeline, will reduce late-stage attrition to improve R&D productivity. In fact, we now estimate that the probability of technical success for our Phase II pipeline is approximately 50%, about double the current industry average.

Could you explain the rationale behind Chorus?

Chorus is a small group of experienced drug developers focused on establishing POC on our drug candidates as quickly and as inexpensively as possible. Chorus operates outside of the bureaucracy of our traditional drug development effort. We purposely pick compounds for Chorus for which POC can be established in small clinical studies. By quickly establishing POC prior to Phase II, Chorus reduces costs, and, most importantly, reduces downstream Phase II and III attrition. We estimate that Chorus increases R&D productivity from candidate selection to POC by as much as 5–10-fold over more traditional pharmaceutical development. According to our benchmarking surveys, Chorus reaches POC 12 months earlier and at half the cost, driving down the cost to POC for each compound from about \$30 million to \$5 million. Importantly, the Chorus model will enable compounds to fail faster — as 80–90% are destined to do — thus saving precious resources for more promising

molecules. However, many molecules return with encouraging positive POC; for example, analgesic activity in human pain models. This type of data helps to reduce Phase II attrition from roughly 75% to 50% as I indicated earlier, and, if sustainable, will by itself reduce the cost of developing a NME by almost \$300 million.

Could you describe the innovative partnerships set up to reduce drug development risk?

We believe that transforming our approach to R&D will be crucial for the industry to survive and flourish. This transformation includes our cost structure and entire approach to partnering. We are moving quickly from a FIPCo (fully integrated pharmaceutical company) to a FIPNet (fully integrated pharmaceutical network). Our emerging FIPNet allows us to leverage our resources by sharing risk with multiple partners, dramatically increasing the number of "good shots on goal." One example of a FIPNet partnership is our recent agreement with Covance to outsource our toxicology work from preclinical to Phase I. Another example is a deal with TPG-Axon and NovoQuest to share the financial risk of our pivotal Phase III AD studies. Also, to better leverage our R&D investments — and because we discover more molecules than we can develop ourselves — we have established several partnerships for external development. Nicholas Piramal India, for example, is developing two molecules that Lilly discovered and, if successful, we can bring them back into our pipeline.

What led to the acquisition of ImClone Systems?

We started to invest more heavily in oncology 6 years ago because the science was evolving quickly. As a result, Lilly has 14 oncology molecules in clinical development and already markets two very successful cytotoxic agents. With the ImClone acquisition we add not only the very successful epidermal growth factor receptor (EGFR) antibody cetuximab (Erbiximab) to the portfolio but also five other monoclonal antibodies against receptor tyrosine kinases that are compelling cancer targets. This acquisition has amplified our oncology portfolio and we believe that together they provide the substrate for Lilly to become an oncology powerhouse.