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State Of Pharma R&D: Ex-Takeda's Yamada Takes The Long View

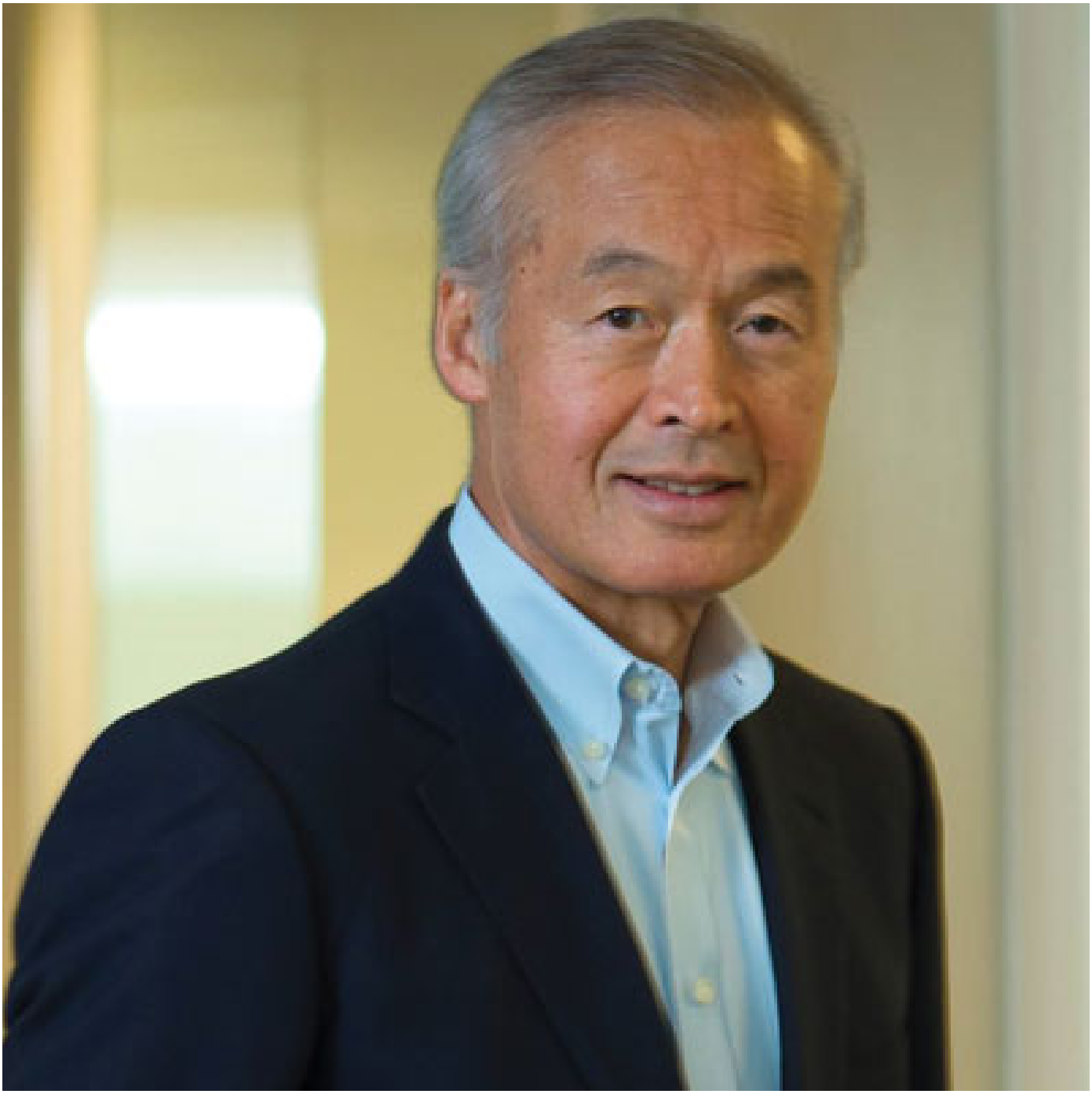
by William Looney

Industry veteran Tadataka Yamada draws on his multidisciplinary background for perspectives on what's new – and what isn't – in a field where every researcher has at some point experienced the same teachable moment: when you strive to make a medicine, so many things can go wrong.

Biopharma R&D today remains a high-interest promissory note on the future of medicine. Redeeming that note periodically with therapies that advance the standard of care allows the drugmaker to survive, to grow – and to renew itself. Yet efforts to "de-risk" the drug pipeline process and render it scientifically and financially predictable have become harder still as the bar to innovation gets higher and more selective.

Deloitte's 2017 survey on returns from biopharma research confirms the long-term decline in the R&D productivity ratio (between capital outlays and cash inflow from sales) among the 12 largest biopharma companies, from an average posted return of 10% in 2010 to less than 4% in each of the last two years.

At the same time, however, there is strong anecdotal evidence of variations among companies in R&D performance – some drugmakers just seem to do better at extracting wins from their pipelines than others. Could it be that where you stand on the overall curve of approved new chemical entities (NCEs) is what counts? And is success the result of random acts of serendipity or is there a replicable formula that raises the odds of success?



Source: Tadataka Yamada

To provide some personal context to the state of today's R&D enterprise, In Vivo spoke recently with Tadataka "Tachi" Yamada, a physician polymath who has worked many sides of the industry's research ecosystem, leading multibillion-dollar R&D programs at *GlaxoSmithKline PLC* and *Takeda Pharmaceutical Co. Ltd.*; heading global health programs for the world's largest private health philanthropy, the Bill & Melinda Gates Foundation; and serving as a member of

the National Academy of Medicineventure partner at Seattle-based Frazier Healthcare Partners. This latter position puts him on the boards of several start-up biotech companies with novel drug discovery platforms linked to recent advances in identifying the biological origins of disease.

Even in his current role as a venture capitalist, Yamada retains his commitment to global health, noting that increased access for neglected populations in resource-poor environments is a great stimulus to product and process innovation, applicable to rich markets as well as poor. In the following Q&A, Yamada looks at what's new – and what isn't new – in a field where every researcher has at some point experienced the same teachable moment: when you strive to make a medicine, so many things can go

Q In Vivo: While R&D performance among big pharma has been mixed in recent years, it is not due to a lack of experimentation – your own record in leading process innovations at GSK and Takeda proves that. What do you see as the most significant changes in the way drugmakers manage the research enterprise to bring promising new compounds to market?

A Yamada: There has been a profound shift toward external sources of innovation as the driver in delivering results from the big pharma pipeline. What was a trickle of ideas from outside only a decade ago has become a flood, and the trend now extends to cooperation with rival drugmakers as well as small biotech, academic institutions, the VC community and even patient groups. Companies are tapping their balance sheets for those transformative M&A transactions, but they are also funding smaller projects with external partners to supplement – or even compete with – internally sourced activities. We are beginning to see an amazing level of cross-fertilization with organizations outside the traditional drug space, as new computational and bioengineered platforms emerge for "virtual" in silico testing that can handle lead generation much faster than the traditional lab-based experimentation involving living subjects.

An interesting approach to externalization is the increasingly popular "build to buy" strategy in which pharma companies will pay a smaller biotech to do the product development work externally and thus avoid the bureaucracy and encumbrances of a large organization model. Then the pharma company will acquire its biotech partner after certain milestones have been met. Recently, I helped broker a deal between a

start-up company, *PvP Biologics Inc.*, led by a team of scientists associated with the University of Washington's Institute for Protein Design, and my former colleagues at Takeda Pharmaceuticals, to help fund a promising compound, *KumaMax,* for treatment of the symptoms and intestinal damage associated with celiac disease. Takeda will provide funding to take this therapeutic candidate through a Phase I proof-of-principle study, a commitment of resources which otherwise PvP Biologics could only have secured under less favorable terms through venture capital. It's an increasingly common example of how innovation today is a collective rather than a unitary endeavor, one highly dependent on inter-disciplinary insights and applications. The trend to redirect resources around a more diverse set of opportunities is certainly stimulating from a purely scientific standpoint. But it can raise tensions in the research organization due to the hard choices involved in addressing areas where externally and internally sourced projects conflict or overlap. On a purely intellectual level, it offers a way out of projects of marginal value whose internal owners are hard to dislodge in the absence of an appealing alternative. More important, competition from outside is forcing big pharma organizations with a longstanding commitment to risk-averse behaviors to begin acting like an entrepreneurial start-up.

That's why I see external R&D innovation as a disruptive game-changer, even if culturally the change in mind-set can be hard to pull off. Nevertheless, companies have little choice but to act as advances in technology challenge the discovery status quo and create more options to speed the move from bench to bedside. Major investments are required to seize these opportunities; some will play out, others will not, and, as often happens in R&D, the downstream payoff may be long in coming. I expect all these forces will combine to hasten R&D's transition from the old "bricks and mortar" infrastructure, along with the heavy investments in human capital required to maintain it, to a smaller, flexible, more open and broadly dispersed model of performance – the new global ecosystem of research.

Q Are there any unanticipated challenges associated with this new emphasis on working productively with numerous outside partners to de-risk up-front development exposures and maximize a compound's potential against

existing standard of care?

A One of the hardest tasks for biopharma companies today is to license-out a promising compound that may not have the best chances to succeed in their own hands. As development costs soar, even the largest drug companies lack the budgetary resources to move all the assets in their pipelines forward to commercialization. Valuing the asset to ensure it is licensed out at an appropriate price by the licensor is harder today because of the unpredictable impact of therapeutic and market volatility within that asset's prospective life cycle. There are dynamic time and duration constraints that complicate the determination of how much – and how long – an asset will deliver the revenues expected from both parties. Also problematic is that business development teams get little credit for this kind of transaction as opposed to in-licensing an asset; to make matters worse, they might even be blamed for underestimating the value of the asset as accrued by the licensee over time.

Q By most measures, R&D, at least among the big pharma players, is failing to deliver the returns expected by investors and society at large. Is this a long-term crisis or simply a transitional situation?

A I believe the criticism of R&D productivity performance is misleading – and a bit unfair. We should start by asking a simple question: what is the ultimate task of an R&D organization within a pharma company? It is to build and maintain a pipeline of compounds sufficient to allow the company to renew itself. On that measure, everyone appears to be doing that, through a combination of internal investments, M&A and deal-making that includes licensing, joint ventures, asset swaps and risk-sharing contracts. Few if any pharma companies have gone bankrupt just because they had a poor track record on R&D. You can even say that the means exist to make every pipeline sufficiently productive to allow a company to survive.

In fact, it's hard to find an acceptable measure by which to evaluate industry success in fighting disease. One benchmark is the number of novel drugs approved by the FDA each year. Until five or six years ago, the numbers were trending inexorably downward, prompting many to bemoan the inevitable death of the pharma industry.

However, in the recent past more new drugs have been approved than ever before. Clearly there are many factors that determine the number of new drugs approved in any given year and it's still premature to predict the demise of our industry.

The challenge of making a new medicine might be exemplified best in examining the fate of two drug development programs that I had the opportunity to participate in. Takeda Pharmaceuticals experienced a long period in which not a single NCE was approved by the FDA. When I first joined Takeda in 2011 I found only one promising asset in the late stages of development, a GPR40 agonist which had the potential to be a first-line oral treatment for type 2 diabetes disease. Analysts forecasted the product to deliver up to $3 billion in annual sales once approved by the FDA. However, near the very end of our clinical trials we encountered three patients with a toxicity signal indicating that severe liver failure might be possible with the drug. This was a safety signal that we had not predicted from our preclinical toxicology studies and we had not observed previously in thousands of patients who had been exposed to the drug. In any case, the risk to patients was sufficiently great that we had no choice but to terminate the drug and forfeit the $400 million we had spent on its development.

Shortly thereafter, we had to confront another potential reversal on a monoclonal antibody treatment for inflammatory bowel disease. The regulators were concerned about the risk for progressive multifocal leukoencephalopathy (PML), an aggressive CNS viral disease, and a side effect seen in an antibody against a similar but not identical target. They required us to confront the question directly through an expensive high-risk trial, that would expand the safety database to 2,000 patient years. This required re-allocation of over $100 million from an R&D budget that had already been set for the year and committed to other drug development programs, most of which were considered to be more promising than the antibody in question, which had always been a stepchild in Takeda's portfolio. Nevertheless, we did exactly that, much to the consternation of many in our R&D organization whose programs were terminated or delayed as a result. Even one case of PML would likely have killed the drug's commercial potential. Yet it turned out that the decision was a correct one

– no cases of PML were detected, the drug was approved and launched under the brand name *Entyvio* [vedolizumab] and it is now a blockbuster, the most successful product in Takeda's portfolio.

These were two cases with diametrically opposite outcomes. One led to abandonment of a potentially great product at a late stage because of a toxicity signal that only emerged at the very end of Phase III – data from the two earlier phases revealed no such signal. The other was a gamble we took to commit to answering a question of potential toxicity that, had it been borne out, would have certainly inhibited the prescribing of the drug by physicians. The gamble paid off and finally handed Takeda a well-deserved win.

What these two case studies demonstrate is that human biology is never completely predictable. Inherent scientific uncertainty involving complex interactions between biology, chemistry and the laws of physics cannot be willed away with an economics mind-set driven by zero tolerance for risk. The idea that the productivity of biopharma R&D is on a linear path of decline and that this trend can be reversed through one-off process efficiencies is misguided. The more we are able to shed light on some of the mysteries of the human body the more likely we will be able to proceed with greater success in drug discovery and development. Nevertheless, there is an element of serendipity to making new medicines that will never go away.

Q **Looking forward, what do you see as the most exciting areas of new science with the most potential impact on patient care?**

A We are already at the stage where small molecules and antibodies are ceding ground to the potential therapeutic applications from cells and genes, nucleic acids, peptides and small proteins. A fast-emerging retinue of RNA therapeutics will boost the potential of these platforms into new treatments and cures. We will see advances in the design of proteins or peptides, to deliver drugs individually tailored to the disease profile of a patient. I am currently an advisor to the University of Washington's Institute of Protein Design, which has led much of the fundamental academic work in this field. I am helping to translate the institute's fundamental research into early-

stage commercial projects underway at two spin-off companies. One encouraging initiative the institute is pursuing is developing self-assembling nanoparticle-based virus-like particles presenting antigens in a multimeric array to induce immunity against infections. Ultimately, this technology could be applied to address non-communicable diseases such as cancer.

Another area I am excited about is the microbiome. Humans harbor more than 10 times as many organisms in their microbiomes than the number of cells in their bodies. The composition of any one individual's microbiome is unique; that uniqueness will influence what the host person will experience in terms of disease. For example, recent studies showed that the microbiome may play a role in the hypertension induced by excess salt in the diet through specific bacteria that regulate immune cells in the host. Other studies have linked dietary trehalose to the growth of pathogenic *Clostridium difficile* in the gut. What I especially like about this field is the possibility that drugs directed at regulating the bacteria in the gut might be able to address human pathology without exposing the human hosts to the risks of the drugs. The dangers to the patient are inherently less.

Q In addition to managing large R&D operations in the private sector, you have been actively engaged in efforts to raise the industry footprint on global health issues. Why is global health and access to the poor a business issue, beyond mere charity?

A There was little investment by the pharma industry in addressing global health challenges prior to the end of the 1990s, with the exception of Merck & Co. Inc.'s river blindness [onchocerciasis] and SmithKline Beecham's elephantiasis treatment programs. Establishment of the UN Millennium Development Goals along with the efforts of new and larger global health initiatives such as the Bill & Melinda Gates Foundation; the Global Alliance for Vaccines Immunization (GAVI); the Global Fund to Fight AIDS, TB and Malaria; and President George W. Bush's PEPFAR program proved that with proper investment progress can be made against some of the world's largest health problems, even in the poorest countries. The work of these organizations quickly showed that investment in global health delivers a positive

economic and social return. Additional challenges such as the SARS pandemic and the Ebola crisis showed that some problems of the developing world could not be contained in the countries where they started but had the capacity to spread to even the richest countries overnight – no one is immune. Lessons learned from global health initiatives have served to underscore the importance of strong health care systems that promote access to basic care. This is as true for Europe and the US as it is for sub-Saharan Africa. What industry does in resource-deprived settings can carry benefits to rich health care systems by restoring the emphasis on public health and finding better ways to provide products and services at lower cost.

In this context, there are a couple of initiatives that may have important implications for the global pharmaceutical industry. The first is a growing commitment by governments to the idea of "universal health coverage." This loosely defined concept may mean many different things but at its core is the principle that all people should have access to basic medical services – including drugs – that provide therapy for important non-communicable diseases like diabetes, hypertension and even more advanced conditions like cancer. The Clinton Health Access Initiative, on whose board I serve, is now coordinating access to cancer chemotherapy drugs in a number of African countries with support from major drug multinationals like Pfizer. This in turn has expanded interest in new logistics and delivery platforms at a cost far lower than the norm, a development that is worth applying elsewhere as the exemplar of "frugal" process innovation.

The second is how multilateral agency efforts to assess the economic stability of a nation, which have a direct effect on its credit rating, might be extended to rate the commitment and quality of its health systems infrastructure. This arises from the observation that during the Ebola crisis the affected nations lost over 10% of their GDP overnight, while adjacent countries like Nigeria, with better developed health systems, were able to contain the spread of the deadly virus. Such a policy, if enacted by key organizations like the International Monetary Fund (IMF) could lead to rapid growth of upgraded health infrastructures, including a more functional medicines market covering essential drugs as well as more innovative products. Ultimately, even

the poorest nations of the world could become important markets for the pharmaceutical industry if it pays attention to its role in helping to build the heath infrastructures in those countries.

Q **Is there a potentially disruptive issue that you believe will have the most adverse impact on biopharma's overall license to operate?**

A The biggest threat stems from the widening perception that the US innovative industry is becoming irrelevant, a marginal player in health, with products that are largely ineffective and cost too much. Many influential constituencies believe biopharma does little to benefit the average patient, and that the government must therefore step in and replicate the work of the industry on drug discovery and development. The notion that public initiatives can replace the resources, expertise and general know-how of the private sector in bringing a new drug to market is far-fetched. The fact that this is even being contemplated suggests that not much is being done to educate the public on just how hard it is to make a new medicine.

Q **Is the pharma industry accountable for its reputation problem?**

A The challenge is there because of the way our industry has behaved in practice. The evidence is clear: a substantial portion of the industry's growth in recent years can be attributed to jumbo pricing of new medicines and uncontrolled price increases for existing medicines whose innovative attributes have been around for some time. Going forward, pharmaceutical companies must be able to demonstrate the true medical, social and economic value of its medicines in order to justify the price tags attached to them. The industry must be seen as contributors and partners in the effort to enhance the welfare of nations, not predators that only suck out the resources allocated to improving health. It can do this by redoubling its commitment to what it does best, creating innovative solutions for complex medical problems with unmet need. If the industry does that well I have no doubt that it will be appropriately and richly compensated.