



The Innovators

Conversations

on the Cutting Edge

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Interview with Dr. Ward Peterson Senior Vice President, Scientific Affairs Inspire Pharmaceuticals



Dr. Ward Peterson is Senior Vice President of Scientific Affairs and Strategic Interventions at Inspire Pharmaceuticals. His previous role at Inspire was as Head of Research and Preclinical Development. He has over ten years of experience in biotech and pharmaceutical R&D. In recent years, he has developed a keen interest in using decision analysis tools to support strategic decision making at the R&D, business development, and commercial levels. He spearheaded the implementation of value-based portfolio management approaches at Inspire, and has given presentations on this topic at conferences. Dr. Peterson received his Ph.D. in Biophysics at University of California, Berkeley.

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Interview conducted by Doug Berger, INNOVATE doug@innovate1st.com

Doug: Let's start with an overview of the big challenges in drug discovery and development that face Inspire Pharmaceuticals.

Ward: This is a high risk industry. It takes 10-15 years and ~1.3 billion dollars to get a new drug approved. More than 99.9% of new molecules tested in discovery are discarded before one is deemed worthy to enter Phase 1 clinical trials. Even then, this molecule has only a 10-20% probability of ever getting approved. So much time can elapse that the treatment landscape and market conditions for the drug may change dramatically. How to make good decisions in the face of these risks and investments is universally accepted as key challenges.

When so much money is committed in R&D, even early on, it understandable that bottom-line stakeholders such as upper management and investors want a solid business case that they can bank on. Yet many scientists believe that pharmaceutical innovation is so uncertain that it can't be quantified in a spreadsheet. In a way, both camps are right. We recognize that investing in innovation should be analyzed as a business case, but not with the limitations and false precision of, say, an Excel forecasting model. We resolved this conflict by seeking useful tools, processes and know-how that we could apply to our business. To make good investment decisions, we need to adopt a framework that embraces uncertainty and a fulsome view of the value proposition. It should identify factors that drive the upside potential of an asset, just as it should ferret out those factors that destroy value. It should

strike the right balance between a squishy “what my gut is telling me” approach and an overly rigid spreadsheet model approach.

Where I think Inspire was ahead of the curve, especially given our stage and size, was our willingness to introduce forward-thinking approaches to evaluate the business of innovation. A few years ago, we brought in formal framework of Decision Analytics to understand the true value of our assets. It is rigorous, transparent, and leads to company wide buy-in for better decisions.

Doug: You are aiming to create a new paradigm for the investment worthiness of an individual drug under development, and for the portfolio of all drugs.

Ward: We want to make better investment decisions. A trap that people fall into is looking at the decision to resource a particular activity as a stand-alone, yes/no proposition, rather than as trade-offs among other opportunities. Another trap is to derive a measure of value such as an Net Present Value (NPV) based on single-point estimates, without appreciating the range of NPV in upside or downside scenarios. Your view of two assets with the same base-case NPV may be altered if the upside potential of one asset is much greater than the other. The conversation then focuses on “what is driving the upside potential, and how can we capture it?”

But for trade-off and sensitivity analyses to be credible, we need a valuation methodology that allows for true apples-to-apples comparisons across assets in the portfolio. We were able to achieve this by using decision analytics to generate a single, unifying “value map” for our R&D projects, business development opportunities, and even commercial products.

Doug: Are you trying to have business decision making influence how science is done?

Ward: It’s an insightful question because it helps bridge the science of drug discovery and the pharmaceutical business. The conventional wisdom is that science needs to drive innovation. But in reality, business considerations need to factor into the innovation process to generate economic value, not just scientific value.

For example, we can use business thinking to de-risk innovation. Does it make sense to invest to understand the underlying biology of a disease state, in order to identify a target for therapeutic intervention? Some companies pour millions of dollars into this pursuit. At Inspire, we license in patentable biological know-how from academic institutions that developed this therapeutic insight, and we build a drug discovery platform based on it. Three of our clinical programs—cystic fibrosis, dry eye disease, and glaucoma—were based on biological breakthroughs made in academic labs that we licensed in and subsequently transformed into innovative products in development. We get a better ROI with this approach.

So the challenge is to create a decision-making structure based on both science and business that deconstructs the innovative process into dimensions that can realize the value proposition of an asset. This is different from an advocacy-based decision making culture, in which someone advocates a certain decision with a certain outcome in mind. Now we get our scientists and other stakeholders to **focus on the decision dimensions** rather than the decision outcomes. A decision dimension could be identifying the options

for what class of molecules or chemotypes to pursue. A natural product or novel modification? Another dimension may be patentability. Yet another may be choice of biological targets. You end up with decision dimensions that absolutely matter in choosing a drug discovery process. You open up alternatives and options. Which alternative gives us the best prospect of realizing value?

The dialogue surrounding decision dimensions opens up more creativity, allows for more diversity of opinion, and balances different biases. It is also a great communication tool. When you finally make a decision, you have a framework for communicating how you made that decision across these strategic dimensions.

Doug: With decision analytics you are encouraging and/or requiring development scientists to thoughtfully consider and evaluate alternative approaches. Similarly, business people now have to consider different scenarios and options for a good sustainable business. All of this becomes transparent.

Ward: Exactly. Much of the of time decision making is stalled because two camps just can't get past their opposing differences. For example, someone in the management team suggested significant changes to an ongoing clinical study, whereas the R&D team wanted to stay the course. By asking both to "think bigger" and generate additional options, can we create a win-win situation? The answer was "Yes." Some basic decision trees were drawn with clear alternatives and transparent assumptions, and a new solution emerged with a better ROI. There's just much better buy-in on the outcome of the decision.

Doug: Where else are you changing your thinking about managing drug development over the extended timeline?

Ward: In our industry, **decision flexibility** erodes as the product matures in development. A lot can happen during the years of R&D. Our product for cystic fibrosis is currently in Phase 3 clinical trials. It entered Phase 1 in 2000. Over these nine years, the treatment landscape for cystic fibrosis has changed. We need to understand the change and take that insight to question the path that we are on.

Yet, we are very constrained. By the time a program is in Phase 3, you can't change the molecule. It's very difficult to change the formulation, the dosing regimen, dose strength, the clinical endpoints, the device, etc. So, we have to find the sweet spot in developing a product under these constraints while optimizing its medical and business value.

The treatment burden for cystic fibrosis patients has skyrocketed. Patients in the earlier stages of their lung disease progression are taking six, seven, eight daily medications. That wasn't the case ten years ago. So now we're asking, "How do we now think about our product when our target patient population is already spending 2-3 hours a day just to treat their lung disease?" That has led the team to recognize new opportunities for the product.

All 50 states now require genetic screening of newborns for cystic fibrosis, which was far from the case ten years ago. Right now a baby diagnosed with cystic fibrosis is not taking anything to treat their imminent lung disease. Could we delay the disease progression by years, if not decades? Such an early intervention approach would necessitate some additional clinical studies.

Developments over the past decade may have introduced new challenges, but also new opportunities. The business case here may be suggesting some additional studies. Being successful in innovation requires the ability to recognize, react, and adapt to changes, with business and science operating in lock-step.

Doug: Historically, you've had a certain therapeutic aim in mind, and it was fixed over the development life cycle. Now, you want to force yourself into considering a range of flexibility rather than just proceeding as if you were on a rail towards an inevitable area.

Ward: The new insights we have uncovered by appreciating the change in the treatment landscape gives us new opportunities that we're exploiting. Those opportunities may have such a big upside that it could be well worth the additional investment to expand the current development program.

Doug: Can you point to other innovative ways in which you are now going about the process of drug discovery?

Ward: Not only does the treatment landscape change in ten years, the competitive landscape of products in development also changes greatly. We have begun rethinking our product in the context of what it is going to look like when we launch this product. What else will be out there and how do we create a competitive edge? In understanding and embracing the competitive landscape, we have been able to think about our product so that its true therapeutic utility can be tested against potential competition. In doing so, we uncover new therapeutic value.

Doug: In our initial conversation we talked about a very different therapeutic area, dry eye. Where does your dry eye program highlight other things you are now doing differently?

Ward: Dry eye is a very annoying condition. It can result in visual impairment. It is not a disease with a clear genetic basis. There isn't the benefit of the elegant, scientific insight associated with cystic fibrosis. Scientific bridges were built to link the genetic defect in cystic fibrosis and the disease state, so we could design a molecule that we hope could intervene in the disease progression. In dry eye, there were a number of scientific hypotheses, but no real bridge. There is only one drug approved for dry eye and it took several FDA reviews. The condition itself is mystifying because the health of the eye surface doesn't seem to correlate with how well patients feel. Ironically, as you improve the ocular health at the surface, patients don't necessarily feel better. They actually may regain more sensitivity, causing them to feel a little worse. That's something that was never appreciated when we started the program.

The regulatory pathway for approval of a new drug for dry eye was extremely challenging. What we did differently in this example was to forge an alternative development path by generating new scientific insights while our drug was already in late-stage clinical trials. This required working with medical experts and the FDA to come up with a new, clinically meaningful endpoint with which we can evaluate our product. We believe that the new endpoint will be of ultimate benefit to the key customer, the patient.

Doug: Can you reflect on where your own thinking is now as it relates to future challenges, and how you're going to go after those challenges?

Ward: Science and technology are advancing much faster than pharmaceutical innovation. A breakthrough discovery in the laboratory today may not translate into an FDA approved medicine until two or three decades later. To invest smartly now requires foresight into the economics of healthcare many years into the future. While a lot may change during this time, I believe that a golden rule is to invest where the medical need is underserved, even in very small "orphan" diseases such as cystic fibrosis. I think that the approach of licensing in promising technology developed from academia and transforming them into meaningful products will continue to be a successful model for biotech and pharmaceutical innovation. A key concern shared in our industry is the impact of an even slower, more expensive and riskier R&D process, and whether the current intellectual property and patent restoration system provides adequate incentive for investors to support pharmaceutical innovation in the future.

Another way to think about innovation in medicine is to take approved products and find new uses for them. The concept is not new, but I see greater shifting of resources in this area. There are so many creative ways to repurpose a medicine — new delivery systems to target specific organs, new formulations to reduce need for frequent dosing, using pharmaco-genomic insight to "tailor" drugs to specific populations, finding creative combinations of drugs to target new diseases, and the list goes on. This is an approach we are actively pursuing at Inspire. We launched an eye drop product in 2007 that was approved for bacterial conjunctivitis (also called "pink eye"). Pink eye is a well served market, but we have evidence that the active ingredient in our eye drop product may treat inflammation of the eye lid margin (the blepharitis), which eye care professionals say is an underserved market with no FDA approved product.

Repurposing already approved medicines also makes good business sense. It is a smart de-risking strategy. The question here is not *whether* this is an innovative approach, but in what ways can the industry be more creative in identifying new uses for approved medicines? This is where technological breakthroughs in other areas, such as information technology, need to be harnessed. So much data from patient use is gathered once a drug is marketed that a smart player is one who is able to ferret out new therapeutic signals in all of the informational noise.

Many rules of pharmaceutical innovation are changing. Successful organizations are those who can play by the new rules in a volatile landscape to manage the business and scientific dimensions of pharmaceuticals, and develop products with real medical value.

