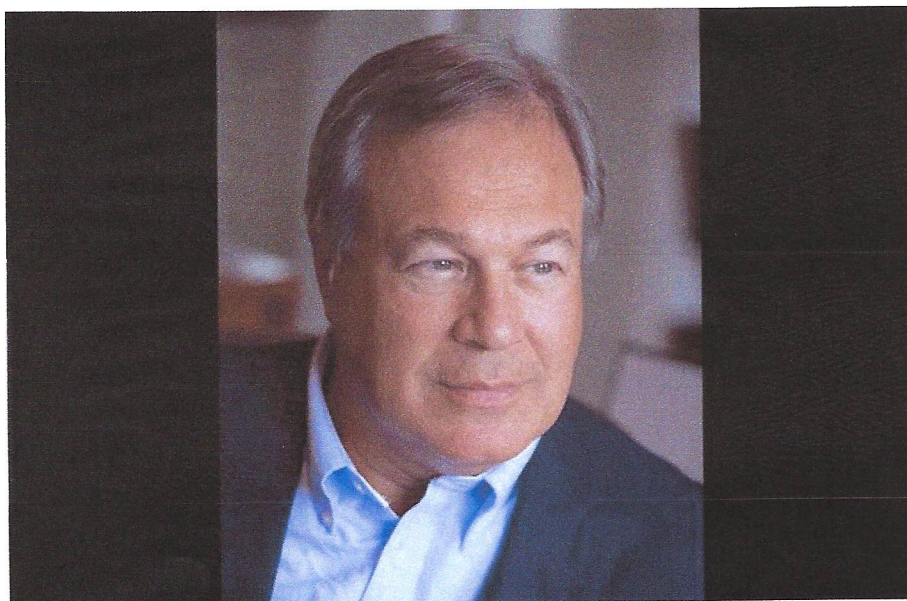


Chasing Invention: Jeffrey Kindler At The Helm Of Centrexion

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Sometimes, this industry creates problems only it can solve. The current opioid epidemic — aka, America's new war on drugs — offers a case in point. If prescription opioids can be lumped together with street drugs such as heroin and fentanyl as a cause of addiction and death, the only logical solution is to withdraw them from the market. If attempts to create abuse-deterrent forms of the prescription narcotics have backfired, let's abolish the concept of chronic pain and give the drugs only to dying patients in the most extreme agony. Or when patients cut off from the meds still insist on whining about their condition, let's offer them the alternative of switching to a lifelong neuropsychiatric drug that, even if it fails to relieve their pain, at least makes them less depressed about it. Or, better yet, maybe someone should just go back to the drawing board and do what the best of the industry does — invent a better drug.

That someone — or some company — may be Centrexion, now led by the former chairman and CEO of Pfizer, Jeffrey Kindler. Centrexion is developing novel agents to relieve some of the worst chronic pain experienced by human beings, without causing addiction or the other adverse effects of opioid medicine.

Hold on, someone who ran a top-five Big Pharma is now heading a biopharma startup? Perhaps the picture is not so unlikely. At his former company, a behemoth formed through many mergers, Kindler dealt with the frustrating conundrum of ballooning R&D budgets tracking alongside plunging R&D productivity. Coming from another discipline and a different industry — he was the head legal executive for

McDonald's and head of litigation and policy at GE — he had joined pharma just as the leading consolidated companies struggled to operate at a much greater scale. Now, at Centrexion, he exemplifies a more recent trend: enlistment of former top executives from the industry's largest companies to manage some of the smallest. Still, from Kindler's vantage point, his career has always turned toward new opportunity, and it has taken him where R&D is actually creating something needed and new — a pure enterprise, chasing invention.

"I had spent my career in very large organizations, and I was really attracted to the opportunity to be involved in a startup environment and its very different culture. I became an adviser and investor in a lot of such companies, and still am, and then the opportunity to get involved in Centrexion presented itself," he explains.

A DIFFERENCE IN PAIN

Like many biopharma executives, however, Kindler had a personal motivation for taking command of a startup. His wife suffers from osteoarthritis, a condition that causes endless, intractable pain for millions of patients. Not even the infamous opioids offer much help with arthritic pain.

"The treatments available today are really inadequate in a lot of ways, whether they be over-the-counter drugs or prescription agents that have various adverse cardiovascular or GI effects; steroids, which have a limited ability to treat over time before they start to produce tissue damage; hyaluronic acid injections, which are not particularly effective; and ultimately interventions such as knee surgery," he says.

"With the opioid crisis, there's just a tremendous need for alternatives. Centrexion is addressing an enormous medical need in a very compelling way, and it was a chance to apply some of the things I had learned and experienced at Pfizer to a new environment."

Kindler says he didn't fully appreciate the scope of the pain problem until he became more involved in the area. He points out that the 100 million people in the United States who suffer chronic pain at some point in their lives amount to a larger population than for cardiovascular disease, diabetes, and cancer put together — and pain-related disability claims cost billions of dollars. Of course, misuse of prescription opioid drugs could add much more in costs to the total. No one can say at this point how much actual relief a potent, nonaddictive alternative would bring to the problem; opioids will not lose their appeal for "extratherapeutic" users. But as opioids vanish from all but the most extraordinary practices, a nonaddictive option could offer patients safer pain relief from the beginning of treatment on.

Centrexion is ready to enter Phase 3 development with its lead drug, coded CNTX-4975, for treatment of knee-osteoarthritis pain and has a pipeline of other candidates and indications moving in parallel or following behind. CNTX-4975 and the other agents inhibit the transmission of pain signals to the brain. Development is focusing initially on localized pain; CNTX-4975 uses the company's STRATI (Synthetic TRans cApsaicin ulTra-pure Injection) technology, which addresses the previously enormous challenge of administering a drug based on capsaicin, the "hot" ingredient of hot chilies.

Past attempts at developing capsaicin-based drugs have run up against the burning sensation they create when administered, which can cause acute, though transitory, pain to a patient. Kindler says Centrexion has taken years to work out a pretreatment procedure that contains the numbing agent lidocaine and involves controlled cooling, taking the sting out of the injection treatment.

The program illustrates a lesson from his experience in Big Pharma — spend time to perfect a compound, formulation, and delivery that improves on treatments in the existing standard of care. Although the search for a solution to the administration challenge began before his arrival, Kindler was well-prepared to appreciate the value of such development in potential ROI.

Any company developing treatments for patient-reported symptoms can take another lesson from Centrexion's experience: Develop drug candidates that yield unequivocal results, based on how they act in the body. Corollary: When possible, avoid entirely the effects that make the current treatment standard unsatisfactory.

“Doing clinical trials for pain can be challenging because you ultimately depend on the patient's subjective view of whether their pain has improved, and often a placebo effect makes it difficult to prove the efficacy of the medication,” Kindler says. “Even more complicating, opioids trigger the pleasure sensations in the brain that create addiction. But our technology doesn't work that way. Our drug is a very selective agent, interrupting the local pain signal. It has a very short half-life and is out of the body in 24 hours. It affects only the local pain nerves and has no activity outside of them. If our Phase 2 results are repeated in Phase 3, our drug will be a profound game changer that allows patients to visit the doctor only twice a year, get an injection, and experience very significant pain relief with no meaningful side effects.”

Unlike opioids, Centrexion's product will not be a scheduled drug, which would require patients to sign a contract with the prescribing physicians and take periodic drug tests. “It will not be scheduled because it has no addictive or dependency issues whatsoever. Based on the evidence today, it's as safe as a placebo,” says Kindler.

So, is it more effective than placebo — or rather, the infamous placebo effect? That turns out to be a challenge on its own. The placebo effect has typically run high in pain trials because patients tend to anticipate relief, especially when injected. Centrexion's chief medical officer, Dr. Randall Stevens, has introduced some clinical trial measures — including careful training of investigators and patients — that help separate the placebo and drug effects significantly, as seen in the Phase 2b results, according to Kindler.

“It is considered a good result in pain trials if 50 percent of the patients experience 50-percent reduction in pain,” he says. “In our Phase 2b trial, nearly two-thirds experienced a 70-percent reduction, and about a quarter of the patients experienced at least a 90-percent reduction. Our patients are coming in having failed other treatments and having a pain score in the 6 to 10 range, or moderate to severe pain, and after the treatment they're down to 3 or less, which is mild or no pain. That's a really meaningful change in someone's life and how they go about their daily activities.”

Other Phase 3-ready programs for CNTX-4975 include a treatment for osteoarthritis in pet dogs and an orphan condition of Morton's neuroma, which was granted FDA fast-track review status. The condition causes extremely painful neuromas to form between the toes. It is especially prevalent among women who wear high heels and marathon runners. The only current treatment is surgical removal of the neuromas, which creates numbness and often leads to eventual relapses.

SINGLE FIELD, FULL PIPE

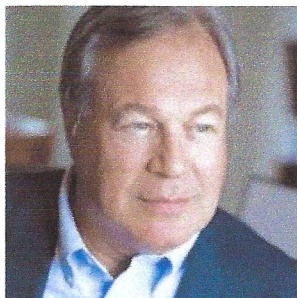
Another possible lesson from Centrexion, Kindler, and perhaps the Big Pharma world: If you want to broaden your pipeline, minimize risk by expanding indications for the same compound or similar ones from the same platform. The company has generally followed that pattern, but it also has shown its willingness to act opportunistically

rather than stick to its in-house STRATI technology. It has purchased three assets from Boehringer Ingelheim: a CCR2 (chemokine receptor 2) antagonist for inflammatory pain, a CB2 (cannabinoid receptor) agonist for neuropathic pain, and an SSTR4 (somatostatin receptor 4) agonist for various potential chronic pain indications. The company also acted in a wholly practical fashion with its lidocaine gel product to fill a gap in treating areas of the body, such as the face, where lidocaine patches work poorly or not at all.

“Each of these is either a first-in-class or best-in-class asset, or both, that is in Phase 1 studies and that we intend to advance,” says Kindler. In early research, Centrexion’s chief scientific officer, Dr. James Campbell, is working on “intrathecal” (spinal-column) delivery of pain medicines for the most severe kinds of pain. “We are developing injectables, small molecules, oral drugs, topicals, and intrathecal drugs. And, we are using many different kinds of delivery systems, but what they all have in common is that they are effective, safe, nonaddictive treatments for chronic pain.”

Rather than try to replace the standard, first-line treatments right off the bat, the company is developing its products for patients who have already tried and failed all standard options, from opiates to OTCs to neurologic drugs such as Cymbalta or Lyrica. The subtext lesson here is develop your product to improve on standard care but avoid challenging Goliath until you’ve beaten lesser foes. But Kindler leaves no doubt about Centrexion’s ultimate aims: “The company we’re building here will answer an enormous medical need for the hundreds of millions of people around the world who suffer from pain every day — chronic pain that affects their lives in terrible ways.” In the rapidly upending world of chronic pain, nothing could be more welcome.

THE SCIENCE-BUSINESS CROSSROAD



BIOPHARMA COMPANIES FORM AND OPERATE AT THE INTERSECTION OF SCIENCE AND BUSINESS. HOW MUCH SHOULD THE CEO OF SUCH A COMPANY KNOW ABOUT ITS SCIENCE, AND HOW MUCH SHOULD ITS SCIENTISTS KNOW ABOUT THE BUSINESS OF THE COMPANY AND THE BUSINESS CHALLENGES IT FACES? JEFFREY KINDLER, WHO HAS RUN A BIG PHARMA AND NOW HEADS THE BIOPHARMA STARTUP

CENTREXION, ANSWERS:

“In one of my other activities, I’m partnering with Roch Doliveux, the former CEO of UCB, to mentor executives in healthcare through the GLG Institute. One of our programs helps scientists become better business people and business people become more conversant in science. In biopharmaceuticals, it’s really important for each of those disciplines to understand the other. I’m not a scientist, but I do feel that I have to understand enough about the science and how it works so that I can make some judgments and decisions — and maybe even more importantly — be able to explain it and articulate it to the public and investors. I’m never going to be an expert on science, but my responsibility is to make sure we’re employing people who are really great at it. I need to know enough to be able to talk to the scientist and evaluate for myself whether their judgments are sound. Conversely, the scientists have to understand that they’re not there just to engage in science experiments, but that we are a business that is trying to create value for not just our patients but our investors, and they have to have some appreciation for how all that works.”

BEST MODEL FOR INVENTION?

HAS SO-CALLED INNOVATION, IN THE BROADEST SENSE, SHIFTED MAINLY TO THE SHOULDERS OF SMALLER COMPANIES, FROM THE LARGER ONES? JEFFREY KINDLER, FORMER BIG PHARMA TOP EXEC AND NOW CEO OF THE STARTUP CENTREXION, IS NOT READY TO MAKE THAT CONCLUSION. KINDLER SAYS NO SINGLE BUSINESS MODEL CAN COVER EVERY OPPORTUNITY OR CHALLENGE.

“We have tremendous advances in science, an enormous need for more cost-effective prevention and treatment, and a very complex healthcare system. The days are gone when any one business model, Big Pharma or something else, could address all these problems in an effective way on its own. What we have today, emerging and getting better all the time, is a collaborative ecosystem where all the different models — academia, the government, Big Pharma, specialty pharma, biotechs — all have their role to play and increasingly need to work together.

“There was a time in the 1930s and ‘40s when each Hollywood studio had everything under one roof, and they churned out movies, and they didn’t really require any kind of collaboration or partnership. Today the studios put together movies with partnerships and contracted players. I think that’s what’s emerging today in biopharma. Big Pharma has a very important role to play. It has scale and resources that smaller companies don’t have. It has the ability to commercialize, especially in larger therapeutic areas in ways that small companies can’t. It’s able to take a lot of risks because of the diversity of assets that it has. But smaller biotech companies like ours can bring real focus and attention to particular areas that sometimes are harder to achieve in a large organization. There is an important role for both of them to play, and it’s just that much more important that everybody work together in a collaborative ecosystem.

“It is interesting to see how many former Big Pharma CEOs like myself, Jeremy Levin, Deborah Dunsire, or Chris Viehbach, have gone on to running smaller biotechs. There is nothing as effective in understanding the healthcare system as working at a large company like Pfizer, which participates in so many different therapeutic areas and engages around the world with so many different players in the healthcare system. It is an incredibly valuable set of experiences and is really hard to duplicate in a small company. The experience and the knowledge that I gained about how the healthcare system works and the role pharmaceuticals play in it is of great value to us as we advance our company, and I wouldn’t trade that experience for anything. But it is a lot of fun now to be in a situation where I can have a much more personal and direct impact on what we’re doing. At Centrexion, we have a fantastic team, but it’s a very small team, and I’m very personally engaged in what’s happening in a direct way that I could not do at Pfizer.”