From Breakthrough to Blockbuster:

A conversation with Donald Drakeman

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In their new book *From Breakthrough to Blockbuster: The Business of Biotechnology*, Donald Drakeman, Lisa Drakeman, and Nektarios Oraiopoulos revisit a question posed by Harvard Business School Professor Gary Pisano about the ability of small, entrepreneurial biotechnology companies to compete against large pharmaceutical companies in a research-driven, capital-intensive, and highly regulated industry. While Pisano in his 2006 book *Science Business: The Promise, the Reality, and the Future of Biotech* found biotech had failed to live up to its promise and that large pharmaceutical companies should turn to their internal R&D because they had the resources needed to produce innovative medicines.

Now, in what the authors call "the first major reappraisal of the biotech industry" since Pisano's, they come to a very different conclusion. They say that since Pisano's analysis, biotech companies have produced 40 percent more of the most important treatments for previously unmet medical needs and have done so at much lower costs than their much larger brethren.

Journal of Commercial Biotechnology Editorial Opinion Contributor Daniel S. Levine, recently interviewed Donald Drakeman about his new book for *The Bio Report* podcast. Drakeman, a venture partner at Advent Life Sciences, was the founding CEO of Medarex, which pioneered the development of the checkpoint inhibitors cancer therapies Yervoy and Opdivo. He is a Fellow in Operations and Technology Management at the Cambridge Judge Business School, and a Distinguished Research Professor in the Program on Constitutional Studies at the University of Notre Dame, and a Fellow of the Royal Society of Biology. A graduate of Columbia Law School, he received a Ph.D. from Princeton University.

Edited excerpts of the interview follow.

JCB: Your new book from *Breakthrough to Blockbuster: The Business of Biotechnology,* to some extent, is a reexamination of a question posed 15 years ago by Harvard Business School Professor Gary Pisano about the ability of small biotech companies to compete against Big Pharma. What did Pisano find?

Drakeman: His analysis, which was really on the early days of the industry, said that the biotech industry was not out-competing pharma, that their productivity was about the same, and that the biotech industry as a whole was loss making on the P&L side of things. He advised Big Pharma that they needed to look to their own R&D labs for their most novel products, because what you needed to innovate was a well-integrated, large-resourced organization that could tell good ideas from bad ideas.

JCB: You call your book, the first major reappraisal of the biotech industry since Pisano's. What did you find?

Drakeman: We found pretty much the opposite. That an industry of highly experience, large companies with well-integrated resources focusing on weeding out the lemons is actually less likely to create genuinely novel medicines than the thousands of small independent biotech companies, even though the little companies have never done it before.

JCB: R&D productivity has long been a concern within the industry. While we've seen a range of innovative new therapeutic approaches emerge, there's still a lot of concern about the cost of drug development. As the industry becomes more focused on targeting the underlying causes of diseases and its uses of new drug discovery technologies, such AI, is there any evidence that R&D productivity is improving?

Drakeman: I don't think we're there yet. But there's certainly always hope. The biggest issue in drug development isn't what we know. It's the vast amount of unknown unknowns. If we keep learning at some point, we'll be able to eliminate a lot of those gaps in our understanding, but still, as we suggest in the book, it really takes a lot of attempts, most of which will go nowhere, to be able to find the few that are really, truly new, important medicines.

JCB: You talk about the pharmaceutical industry versus the biotech industry. I think those terms had very specific meanings that have changed over time. How are you distinguishing between a pharmaceutical company and a biotech company today?

Drakeman: We're really not making any distinction based on whether it's a biological molecule or a chemical entity. We're focusing on a definition that the academic communities have used for a while. It seems to make sense. It's any drug development company founded since Genentech's founding in 1976 is a biotech company. And anything before that is a pharma company. There are about 5,000 biotech companies at any particular time, although it's rarely the same 5,000 as companies get started, companies go out of business, or are acquired. And the pharmaceutical industry is about a hundred companies, although with all their resources, 70 percent of those resources are spent by the 12 largest companies.

JCB: In comparing innovative output from pharmaceuticals versus biotechs you compared the number of FDA priority review approvals between the two and the average cost. What's the case for using that as a metric and what did you find?

Drakeman: What we found is that biotech created 40 percent more of those priority review products, 138 of them, to 99 for the pharmaceutical industry. And they did so while spending less. It cost biotech about a $1.5 billion per product, less than the pharmaceutical industry as a whole. And the priority review products, we think, are really the key place to look. It means that the FDA has made an independent determination that this new product offers an improvement in the treatment of a serious condition. That's what we believe that people think of when they think of medical breakthroughs—something that treats disease in a way that we've never been able to before. It's not me-too. It's not extended-release formulations. These are brand new drugs doing things that medicine has not previously been able to do. And most of the top-selling drugs were first approved as priority review products. They have a big commercial impact, as well as a medical one.

JCB: You make an argument about decentralized decision-making leading to greater innovation and promote a framework for improving innovation within a pharmaceutical company. By applying that you describe the biotech industry as a decentralized ecosystem. Can you explain that?

Drakeman: Sure, the 5,000 independent biotech companies are funded by many thousands of different investors, angels, friends and family, venture capitalists, hedge funds, and all of the individuals who buy biotech stocks on the public markets. That means that there are thousands of people deciding on what research and development programs are going to get funded. As a result, many things get resources, many little companies get something from an angel or venture capitalist, the public that would not pass muster if it was up in front of a big pharma review committee altogether. The industry, as a result, has initiated nearly 40,000 different projects during the period we studied, which was from 1998 to 2000. An enormous number of things are tried now, as I think anybody in the industry well knows. Venture capitalists and Wall Street investors are also not shy about pulling the plug if things aren't going well. If you're going to try 40,000 things and only about 140 succeed, that means a lot of plugs get pulled. And that ability to try something and then immediately decide not to keep doing it if it's not looking good, has created a very efficient system for trying lots of high-risk new things, some of which have changed modern medicine.

JCB: How would you contrast that to the way decisions are made within a large pharmaceutical enterprise?

Drakeman: We've worked with large pharma and we also interviewed a number of senior executives at Big Pharma. And what becomes clear is that the R&D resources are allocated by a fairly small central committee. Remember that there are 12 companies spending 70 percent of the industry's resources. Twelve committees are deciding on where the lion share of pharmaceutical research funding goes. And a lot of work goes into weeding out the things that are perceived as bad ideas, things they think aren't going to work. And it turns out that the process that weeds out crazy sounding ideas that don't work also weeds out crazy sounding ideas that do work. And, as a result, pharma only initiated about 8,000 projects during the time period that biotech started 40,000. Once you basically narrowed the pool down to what you think is likely to work, those projects just keep on going. As one pharma veteran told us, when a project gets the green light, it takes an act of God to stop it. And that's why they end up spending more to get less.

JCB: You talk about environments with high ambiguity, which you contrast to environments that are uncertain. What makes a high ambiguity environment? And what's the significance of this within the context of innovation.

Drakeman: A high ambiguity environment is one where not only is there a low likelihood of success, but there are no reliable ways to predict what might succeed or what even the attributes of that success will look like. That's basically a description of innovative drug development. An uncertain environment is different. You might not know that your drug is going to work, but you can make some reasonable predictions based on testing or other things that allow you to make fairly good choices. So that could be a second in class drug, a me-too drug, the checkpoint inhibitors, which is something that the company that I started, ended up developing, were one of those where nobody believed in it, who knew whether it was going to succeed? Releasing the emergency brake on the immune system sounds like an indirect way of treating cancer, but it turned out to be a big success and all the pharmaceutical companies that turned us down for partnerships now have their own follow-on products targeting the same molecules. But they know a lot more about those molecules because we tried that crazy idea that they didn't think was going to work at the time. That's really how to see "uncertain" versus "ambiguous." And ambiguous, the economics literature, the mathematical models have shown for decades that you need to try a lot of things in parallel. In the case of the biotech industry maybe 40,000 things in parallel.

JCB: You outline an innovation strategy you call "SMART," an acronym for Selectionism MAkes Research Transformative. Can you explain what you mean by that?

Drakeman: I know that's a mouthful, but SMART sounds good. It is just another way of saying trying lots of things in parallel or taking a lot of shots on goal as you do things in parallel, instead of in series. We recommend, especially for large companies with big research budgets like Big Pharma, it would be a good idea, or a smart idea if you'll pardon in the pun, to try many more things in parallel and then be prepared to fail early and to fail often. If they can do that, then they have a chance to be more productive, more innovative. And if they fail fast enough, more efficient at the same time. As it is, despite growing research budgets, the 15 largest pharmaceutical companies have not increased the numbers of new projects that they start every year for at least 20 years. And that's about 700 projects. They might source them from different places. They might have more coming in from biotech companies or academia than in house, but it's basically been 700 new projects every year for 20 years. To be innovative will take more than that.

JCB: Years ago, the industry was readying for what was known as the patent cliff, when a large number of blockbusters were heading towards patent expiration. There was a lot of hand wringing over the lack of R&D productivity, among Big Pharma and a move to change drug discovery—notably GSK funded small research groups as if they were independent biotechs. And increasingly Big Pharma has externalized drug development, collaborating closely with academic centers and independent research institutes or small biotechs. How does this compare to your SMART framework?

Drakeman: It's absolutely the right idea, but they need the courage of their convictions. They have typically kept the resource allocation decision-making at the corporate level. They've got all these different places they're getting ideas, but still, they have that central committee that decides which among all those ideas are going to be among the 700 that get new funded. And they haven't increased the overall number of projects. As one former senior executive at a very large pharma told us, "My company tried that decentralization for a while, but then abandoned it because the labs were choosing to do things that management thought was too risky."

JCB: You use the example of the COVID 19 vaccine to illustrate the difference in the ability of Big Pharma and biotech to innovate. Can you explain?

Drakeman: That's a great example. GSK was the world's leading vaccine company. They had mRNA technology in house where their vaccine researchers were working to develop mRNA vaccines on the research lab basis. The lab head asked for approval to use it to develop a COVID vaccine. And that proposal for funding worked its way up through multiple committees. And ultimately, they were turned down because top management said that technology was not ready for prime time. Meanwhile, too little biotech companies, BioNtech and Moderna, just did it. They designed the vaccines over a couple of days and $50 billion in vaccine sales later, GSK isn't the number one vaccine company anymore. It wasn't a technology issue. It wasn't a resources issue. It was how willing are you to try something that hasn't been done? And that's where the little biotech companies with investor funding could do it. And the Big Pharma, with a thoughtful committee of experts, looked at it and said, "It's not worth the risk."

JCB: How does Pfizer's role in the COVID vaccine fit into your model?

Drakeman: Well, they too looked at the idea of an mRNA vaccine and their in-house experts said that it wasn't going to work out, but then when it did work out, they were able to identify a little company that needed more of the D side of the R&D equation to make it happen. They partnered up with BioNTech and I think that we've seen that happen a lot in the industry, although early days it was very common for biotech companies to do the R and Big Pharma to do the D. What we discovered in our data set from the basically early 2000s to fairly recently, is that most biotech companies are keeping their projects either in house or within the biotech industry. They might partner with a larger biotech company, or they'll develop it fully on their own. And that's the example with Moderna. Moderna was able to take it all the way as an independent company. BioNTech found a partner and the value is for all of us.

JCB: Although I guess that that's enabled by the fact that you have these large biotechs these days with the capital resources that used to be the sole domain of Big Pharma.

Drakeman: Yes, a combination of big biotechs with large resources with the fact that that investors, particularly public investors, have been far more willing to invest large amounts in public biotech companies than in the early days. It's not unusual to see companies now with projects in say clinical trials, but nowhere near approval to be able to raise hundreds of millions of dollars. There is an essential thing in the drug development industry, along with the molecule, and it's the money that it takes to develop it. And pharma provides important cash resources, as well as often, as in the case of the COVID vaccines, some development capabilities on the side. Because of the growth of the CRO industry, biotech companies that are able to access the cash elsewhere as Moderna did, have the ability to develop drugs all the way—research through commercialization—without having to rely on the non-cash resources of pharma, which is an area in which the industry today is quite different from the industry in Professor Pisano's study.

JCB: Is there any real impetus for Big Pharma to become more innovative? Can they just rely on biotech and buy their innovation as needed?

Drakeman:

That's an interesting question. And it will end up being determined by just how expensive things get. If the capital markets continue to see fully-independent biotech companies like Moderna and others, who are able to go from discovery to profitability without being bought by Big Pharma or without partnering, with Big Pharma, then the price of buying that innovation from biotech will go up and pharma will then need to either spend more to acquire external innovation, or it will need to figure out how to be more innovative internally. I think maybe there'll be some of each.

JCB: You've been a biotech entrepreneur, a CEO, a, a venture investor. How did your own experiences shape what you were trying to do with the book?

Drakeman: This is just a wonderful, fascinating, complex, and often extremely frustrating business. And it's full of really smart, super-dedicated people who are trying to turn these breakthrough scientific discoveries into blockbuster medicines. They're trying to do two things that are really hard: one is to create a new medicine and the other is to create a successful business. And when you put that together, it can often feel a bit like, as I used to say, playing three-dimensional chess outside in a windstorm. It's a lot of moving parts and a lot of them move without you doing anything about it. The three of us as authors have had the chance to study, to understand, to participate in, to kind of live the process of developing important new medicines. Our hope was that we could help others get a better sense of what all of that was about. It's important for humanity and important for business. It's an exciting story and that's what we set out to talk about.

JCB:

Having written the book, does this change your thinking at all as a venture investor today?

Drakeman:

It helps me see just how important putting entrepreneurs and investors together is in the process of medical innovation. If you think about it, academic labs, pharmaceutical companies, and government researchers all have access to the same technologies, the same equipment, and often more expertise than biotech companies. What has made the biotech industry as a whole different is the partnership of thousands of entrepreneurs and thousands of investors that has led to more new medicines than any Nobel prize winning discovery. Having been both the entrepreneur and the venture investor, it's exciting because it is that combination that has really worked in this particular field.