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Microbiota Restoration Therapy

Powerful therapy, delivered.

What's Next for the Microbiome: View from Industry

The human microbiome has generated a lot of excitement around its potential to treat disease. Papers about the human microbiome are being published at an increasing pace, some holding out the promise of providing answers to vexing medical problems such as *Clostridium difficile* infection (CDI), autism, Parkinson's disease, multiple sclerosis and others. Enthusiasm about the promise of the microbiome extends from the halls of academia to the living rooms of everyday people. Not a week goes by without a big microbiome story appearing in the mass media. The risk of distorted reality is a very real possibility. A word of caution is needed because these new therapies have not been proven safe and effective.

Many medical therapies that seem exciting at first ultimately fail to deliver on their initial promise. To take but one example, consider stem cell therapy to treat heart failure. Despite much enthusiasm about early phase study results, a recent critical analysis has raised questions about the therapy and the credibility of regenerative therapy as a whole.
As the CEO of Rebiotix Inc., a privately held clinical-stage biotechnology company that is working to develop a next-generation fecal microbiota transplant (FMT) drug for recurrent CDI, I can make recommendations based on personal experience that could improve collaboration between academia, industry and government and potentially speed development of therapies to improve human health.

Rebiotix, founded in 2011 in Roseville, MN, is the leader in the new microbiome industry and the first company to bring a human microbiota-based product through the FDA for any indication. The company's lead product, RBX2660 (microbiota suspension), is a live microbial suspension used to treat patients who have suffered from repeated episodes of CDI. As you have pointed out in your RFI, there is precedent for harnessing the human gut microbiome to treat CDI. "In a remarkable clinical trial, patients who were extremely ill due to C. difficile infection returned to full health when they received transplants of a donor's healthy microbiome." However, we must note that this trial was just the beginning of work to prove the safety and efficacy of FMT for recurrent CDI. There is much more work to do.

After a collaborative vetting process with the FDA, RBX2660 was categorized as a drug under the jurisdiction of the Center for Biologics Evaluation and Research (CBER). The company then began a structured clinical research program required to gain FDA regulatory approval. Subsequently, Rebiotix successfully completed an open label

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safety study and is currently conducting a first-of-its-kind, double blind, randomized placebo controlled multicenter safety and efficacy clinical study of RBX2660. The company received Fast Track status for RBX2660 and has also obtained an Orphan Drug designation for the drug. We anticipate being the first company to have an FDA-approved microbiome based product for the treatment of recurrent CDI. This has not been easy and has been confounded by the FDA's own policies.

Clinical research is the tried and true process that has been used for decades by clinicians and companies seeking to develop new drugs and other medical products. It's understood as the only way to advance scientific and medical knowledge, and the only way to discriminate between the excitement of early promise and the reality of true safety and efficacy. We understand this framework well and are moving along as quickly as possible toward completion of controlled clinical studies with a standardized microbial product.

However, we must also call attention to the challenging regulatory environment that currently exists. At a public workshop held May 12-13, 2013 in Washington, DC during which Rebiotix presented, CBER announced its decision to regulate FMT as a drug. Per the agency's normal practice, that meant obtaining an IND prior to using FMT with people. However, after public comment from physicians and patients, the FDA reversed itself and reported that it would practice enforcement discretion. The intention was to enable doctors to treat their own patients without requiring individual physicians to get an IND. However, this policy of selective enforcement has created a "Wild West" environment in the microbiome space. It has led to a situation where at least two corporations are manufacturing, promoting, widely distributing and selling an unapproved drug with no regulatory oversight. At the same time, the FDA has selectively required companies, such as Rebiotix, to conduct the appropriate clinical studies for product registration for future commercialization. In our case, it has cost our start-up millions of dollars and created a difficult competitive environment for recruitment of clinical study subjects. In essence, the FDA's own policies are getting in the way of collecting the safety and efficacy information that the fledgling microbiome industry needs to build a solid foundation for the future.

As we have seen time and again, from the fight against AIDS to the recent rush to develop treatments for Ebola, there are no short cuts around clinical research to develop safe and effective drugs and therapies. Rebiotix is dedicated to gathering the clinical data needed to support future microbiome therapies. We ask that that the FDA and other governmental agencies create a level playing field through the appropriate

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use of regulation that promotes collaboration between academia, industry and clinicians in the costly and time intensive processes required to develop translational microbiota-based therapies for human health. Appropriate regulation of microbiome-based drugs sets the stage to gather real safety and efficacy data for new clinical indications and to avoid the risk of inflated expectations.

We all know friends or family who suffer from diseases, such as CDI, and we wish we had the magic formula to cure them. Fecal transplants may seem like the miracle cure, and we hope it turns out to be the case. However, to ignore the proper regulatory process, even out of good intentions, is not the right thing to do and calls to mind that old proverb: "The road to hell is paved with good intentions."

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