Fecal transplants to follow FDA rules

US Food and Drug Administration (FDA) officials in April declared that fecal microbiota transplants (FMT) will be considered and regulated as biologic drugs. Anyone conducting such procedures is now required to file an investigational new drug application (IND). Although this regulatory change began taking shape two years ago, the April announcement brought forth critics and fans. The latter see this regulatory stance as perhaps enhancing prospects for companies developing products within this particular microbiota-related R&D space. But physicians currently evaluating FMT in patients express frustration as well as outright anger with FDA.

"FDA determined that fecal microbiota meets the definition of a drug and a biologic product and an IND is required to conduct studies in humans, even when [investigators] are not planning to develop a commercial product," says Jay Slater, director of the Division of Bacterial, Parasitic and Allergenic Products within the FDA Center for Biologics Evaluation and Research. "Defining the product is nontrivial, such as what are the active ingredients, potency, stability and consistency." FDA also says that, as it develops guidelines, it will exercise "enforcement discretion" when dealing with physicians who find the IND path burdensome so long as they obtain "adequate informed consent" from patients.

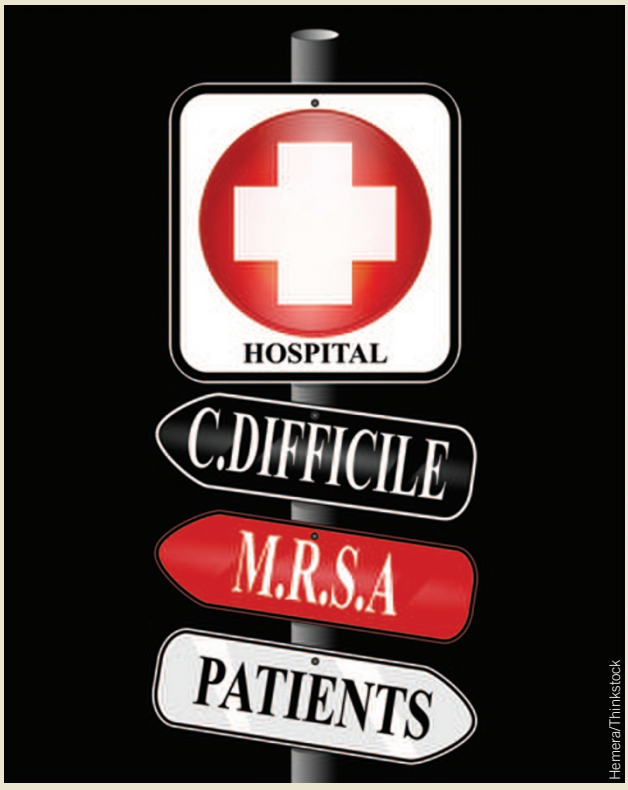
The first concern is safety, with a focus on identifying pathogens that might be present in donor samples for FMT, according to Phillip Tarr of Washington University School of Medicine in St. Louis. Another concern is that such material might carry antibiotic-resistance determinants. If not controlled, those or other risk factors could compound the clinical problems of patients with severe diarrhea caused by *Clostridium difficile*, the infection for which FMT is now being evaluated.

Several university-based investigators who are working with such patients say that, instead of INDs, they would prefer that federal officials establish a patient registry to track any adverse effects of FMT. David Berry, co-founder and chairman of Seres Health in Cambridge, Massachusetts. "A registry would be a step in the right direction, but would not give the same safety benefits to patients as an IND." The company, which is not pursuing FMT but is interested in microbiota and human health, sent more than half-a-dozen representatives to a workshop convened by FDA and National Institutes of Health officials on May 2 and 3, in Bethesda, Maryland.

For physicians, the prospect of agency oversight is daunting, says Colleen Kelly of Brown University Women's Medicine Collaborative, who holds two INDs for FMT clinical research. "When I was told I had to get these INDs, I had absolutely no idea where to start. FDA is used to dealing with companies and industry and regulatory experts, not people like us," she says. Kelly believes the way forward is standardized products, and this will probably happen through industry.

"We're creating an off-the-shelf product, [and] we are the first company to apply to the FDA for a microbiota restoration therapy product," says Lee Jones, who is CEO of Rebiotix in Roseville, a suburb of Minneapolis. "Our IND runs to 1,500 pages and it took more than one year and $2 million." The company's intellectual property position is "strong," she adds, and further helps to give it a "head start" over competitors.

Other companies have competing products to treat patients infected with *C. difficile*, whereas still others are developing



Hemera/Thinkstock

them. For instance, ViroPharma of Exton, Pennsylvania, markets an oral version of vancomycin, an antibiotic used for treating such patients but whose overuse can lead to such infections. The company's VP20621, a nontoxin-producing strain of that bacterium, which is in a phase 2 clinical trial, could be used much like FMT to recolonize the gastrointestinal tract and alleviate such infections. The company declined to comment on FDA's approach to regulating FMT.

Monarch Labs of Irvine, California, currently a supplier of FDA-approved maggots for medical use, in June announced plans to commercialize FMT products. "Monarch is seeking to be a controlled supplier of CGMP-processed FMT material," says its chairman James Kuo.

But companies commercializing FMT products will face a series of unknowns. "We deal with antibiotics and understand the regulatory process pretty well," says Barry Eisenstein of Cubist Pharmaceuticals in Lexington, Massachusetts. In 2011, FDA approved Dificid (fidaxomicin), a macrocyclic antibiotic jointly marketed by Cubist and Optimer Pharmaceuticals of San Diego, for treating *C. difficile* infections. For FMT, however, "There seems to be a continuum from the nonphysician home brew to the doctor's office to the more standardized medical centers to a product from industry to a mixture of well-defined components [bacterial cultures] that could be put together," he says. "Going from one end of the continuum to another, you're getting increasing standardization and opportunity to better study and understand potency, efficacy and safety—and, also, opportunities to commercialize. How [does FDA] regulate the individual at home who calls one of the gastroenterologists and tries to get some advice? I don't understand how that works."

FDA officials admit to confusion on that score, too.

Jeffrey L Fox