INDUSTRY NEWS

FDA Wants Safer Cancer Drugs, but Some Startups Fear Unintended Consequences

Companies developing cancer drugs wrestle with 'Project Optimus'

By Brian Gormley

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The Food and Drug Administration's Project Optimus requires companies to re-examine how they set doses of cancer treatments. ILLUSTRATION: ISTOCK

For decades drugmakers have taken a more-is-more model when dosing cancer drugs in clinical trials. U.S. regulators want them to reconsider that approach.

Companies with cancer drugs in clinical trials must strike a balance between doses high enough to thwart tumors, but low enough to avoid intolerable side effects.

For years, Food and Drug Administration officials have expressed concern that cancer drug doses are often too high, leading to unnecessary side effects. An FDA

program launched in 2021, Project Optimus, requires companies to re-examine how they set doses of cancer treatments.

This typically involves larger clinical trials to test doses to find those that optimally balance safety and efficacy. Entrepreneurs support the aim, but some fear the initiative will add time and cost to drug development, putting startups at a further disadvantage to larger competitors.

“I don’t think anybody disagrees with the idea that we’re trying to find the best thing for the patient,” said David Bearss, chief executive of biotechnology startup Halia Therapeutics. “I hope it doesn’t have unintended consequences of actually suppressing innovation.”

The FDA says it encourages drugmakers to discuss dosing plans with the agency and that new medications can still be brought to patients quickly.

“With adequate planning, drug companies can accomplish dosage optimization and also expedite development of new safe and effective cancer therapies,” an FDA spokesperson said.

Craig Bleifer, a pharmaceutical lawyer and partner with law firm Akin Gump Strauss Hauer & Feld, said Project Optimus likely wouldn’t change after the November election because it isn’t as contentious as other issues, such as drug pricing.

Companies have long determined cancer drug doses by testing small amounts in initial clinical trials and increasing them until they reach the highest level patients can tolerate. Companies then test the so-called maximum-tolerated dose in subsequent trials.

The approach goes back decades to the discovery of chemotherapy drugs that kill rapidly dividing cells—cancerous and healthy. Toxic side effects were a surrogate for efficacy: if a chemotherapy wasn’t harming healthy cells, it probably wasn’t hurting tumor cells either.

Over the past two decades, drugmakers shifted to focus on treatments such as molecularly targeted medicines aimed at proteins overabundant in tumor cells, or molecules these cells overly depend on.

Because these medicines work differently, the maximum-tolerated dose can cause significant side effects without treating tumors more effectively, said Michael Fossler, executive consultant and vice president with Cytel, a contract-research organization serving pharmaceutical companies.

“If you give anything in a high enough dose you will get toxic off-target effects,” Fossler added.

As these newer medicines proliferated, doctors, patients, researchers and others called for a rethinking of cancer drug dosing. A 2013 issue brief by the nonprofit Friends of Cancer Research, for example, noted the need to develop cancer treatments quickly often has taken precedence over finding optimal doses. It called for randomized dose-comparison studies.

A 2021 New England Journal of Medicine article, authored by FDA officials, also challenged the “more is better” model, citing cancer medicines whose doses or schedules were modified, after approval, to make them safer or more tolerable.

Project Optimus launched that same year, with a goal of pinpointing optimal doses before new cancer drugs reach the market. The FDA issued a draft guidance for industry on how to comply with the program in January 2023 and published a final guidance on Aug. 9.

Because Project Optimus is still relatively new it will take a while for its full impact to be known. But it will likely add six to 12 months to the drug-development process, said Tara Raghavan, a pharmaceutical patent lawyer and partner with law firm Benesch Friedlander Coplan & Aronoff.

Lehi, Utah-based Halia hasn’t used the maximum-tolerated dose model in its development of a potential blood-cancer medicine. Instead, the company last year completed an early-stage study in which it tested several doses to identify levels required for the drug to interact effectively with its target protein in the body, according to Bearss. The second-lowest dose tested had the maximal effect, he said.

Halia is now in midstage, or Phase 2, studies in India. When it is ready to extend the research to the U.S., the company will argue it already has identified the

smallest-effective dose and testing additional doses shouldn't be necessary, Bearss said. Halia expects to make its case to the FDA later this year.

After a $30 million venture financing in January, Halia has funding for two Phase 2 U.S. clinical trials, one in cancer and one in another indication outside cancer. Its budget, however, assumes the mid-stage cancer trial will test only one dose. If two or more are required, Halia would have to consider other options, such as raising more capital or focusing only on diseases outside cancer, Bearss said.

"I'm all for trying to make things safer for people," Bearss added. "As with almost every regulation, I want us to be thoughtful about how this gets implemented."

Drugmakers often incur direct costs of about $150,000 per patient in U.S. clinical trials, said Ron Weitzman, an oncologist and consultant to biotech companies. Well-funded biotechs will be able to shoulder the additional costs, but some may be forced to sell or out-license drugs before they want to, he said.

Companies that make it through the process could benefit. Increased communication between the FDA and industry should improve medicines reaching cancer patients, said James Bauersmith, vice president, translational sciences for UPMC Enterprises, the innovation, commercialization and venture arm of UPMC, the Pittsburgh-based healthcare provider and insurer.

"It allows you to go out with what will be a better product," Bauersmith added.

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