Longer exclusivity sought for fixed-dose drug combinations

Momentum is growing in the movement for combination drugs to have longer protection against generic competition in the US. Since January, three drug companies have filed petitions with the country's Food and Drug Administration (FDA) asking the agency to reevaluate its long-standing position that fixed-dose combination pills must contain all-new active ingredients in order to be eligible for five years of market exclusivity, instead of just three. And last month, Jason Chaffetz, a Republican congressman from Utah, introduced a bill in the US House of Representatives that would extend the five-year exclusivity provision to all new fixed-dose drug combinations, even those composed entirely of previously approved ingredients, so long as there's new clinical efficacy data to support the combo product's approval.

"The lack of adequate incentives under current law makes it extremely difficult, if not impossible, for companies to raise the capital necessary to pursue the development of new combination drugs," Chaffetz said in a statement. "This proposed legislation to create additional incentives is good public policy both economically and scientifically."

To encourage drug development, the FDA currently provides all brand-name pharmaceuticals with a limited period of protection from direct competition with generics. However, the duration of protection varies for different kinds of medicines. New chemical entities, or NCEs, which contain no previously approved active ingredients, get five years of market exclusivity, whereas new formulations of existing drugs get only three. (Drugs for rare diseases, pediatric populations and certain infectious diseases can get even longer exclusivity periods.)

Historically, combination drugs that contain both new and previously approved active substances have fallen into the reformulation category. As the argument goes, a medicine of this sort involves a new spin on an old ingredient and therefore the combination does not count as a NCE, regardless of any novel components in the mix. This interpretation had gone unchallenged since Congress first empowered the FDA with the ability to award exclusivity periods under the Hatch-Waxman Act of 1984, which amended a section of the Federal Food, Drug and Cosmetic Act. But on 8 January, drug companies began to speak up.

That day, Gilead Sciences of Foster City, California, openly questioned the FDA's interpretation to grant only three years of exclusivity to the company's anti-HIV/AIDS pill Stribild, which contains two previously approved off-patent antiretrovirals and two newer agents. Three weeks later, New Jersey's Ferring Pharmaceuticals voiced similar concerns about its colon-cleansing drug Prepopik, which contains three ingredients, one of which is new. And in April, Bayer HealthCare Pharmaceuticals, also headquartered in New Jersey, joined the petitioning club, requesting longer exclusivity for its contraceptive Natazia, which contains an older form of estrogen and new kind of progestin.

All three companies claim that the FDA's existing approach to combination drugs is contrary to the spirit and letter of the Hatch-Waxman statute and that it produces outcomes that disfavor combination drug development. Ken Phelps, president and chief executive at Camargo Pharmaceutical Services, a consultancy based in Cincinnati, Ohio, that specializes in new drug applications for these kinds of products, is sympathetic to the drugmakers' point of view. "Why does adding a non-NCE to an NCE make it not an NCE?" he asks. "All of the sudden you're saying this is tainted? I don't see how it fits."

Kurt Karst, a director at Hyman, Phelps & McNamara, a Washington, DC–based firm dedicated to food and drug law, has a more nuanced perspective. "I can see the points made in the petitions, and I can see how FDA, in interpreting the statute, came to the conclusion to which it has come," he says. "The question ultimately is, 'If FDA denies these petitions and it's challenged in court, what is a court going to think? Is the statute ambiguous or not, and, if it is, is FDA's interpretation reasonable or not?'"

It's all down to interpretation

Rather than appealing the FDA's reading of the law, many companies had previously found a workaround. According to Karst, they would "get approval of the single entity first and then pursue approval of the combination thereafter." The five-year NCE exclusivity on the one drug would then extend to the combination product under the FDA's so-called 'umbrella policy'.

Yet, that's not always possible for all drug products. For instance, the new ingredient in Ferring's Prepopik, a stimulant laxative called sodium picosulfate, is known to be ineffective on its own, and it must be combined with an osmotic laxative to effectively prepare the bowels for colonoscopy. Ferring and the FDA thus deemed it unethical and not feasible to pursue approval for this ingredient as a standalone agent.

Piotr Pawinski / Alamy

Exclusivity club: Combo drugs could get five years.

Ferring does have patents covering certain preparations of sodium picosulfate that extend through 2028. But whereas patents like these can be challenged in court, market exclusivity cannot. "Even if the patents go down, you still have this three- or five-year exclusivity," explains Gregory Dolin, codirector of the Center for Medicine and Law at the University of Baltimore in Maryland. "That's essentially unchallengeable," he says. "It's pretty ironclad."

Awarding NCE-length exclusivity to products such as Prepopik or Stribild might only require a re-interpretation of existing statutes—either by the FDA or the courts—but what Congressman Chaffetz has proposed goes much farther. His Combination Drug Development Incentive Act of 2013—introduced with two Republican cosponsors and then referred to the House Energy and Commerce committee on 2 August—would add a new clause that, starting next year, would explicitly lengthen exclusivity to five years for all fixed-dose combinations, even those without a novel ingredient.

"That's a bold request," and one that could dramatically affect the pharmaceutical industry, says Ken Phelps. If it becomes law, "it would definitely increase the number of combination drug products out there. That's for sure."

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