

"The Pink Sheet"

Bill Proposes Offering Exclusivity For Novel Drug Co-Development

The Pink Sheet

By Emily Hayes

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Executive Summary

Bill proposes six months' extra marketing exclusivity to spur development of combinations of investigational drugs for serious diseases. Setting aside prospects for passage in an election season, the question is whether that will be enough to get pharma to buy into a risky development space and pioneer a new business model.

The pharmaceutical industry could see an additional opportunity for exclusivity under recently introduced legislation for novel drugs developed in combination to treat life-threatening diseases.

The legislation –the Life-Threatening Diseases Compassion Through Combination Therapy Act of 2012 – was introduced to the House of Representatives on Sept. 21 by House Energy and Commerce committee member Brian Bilbray (R-CA) with Carolyn Maloney (D-NY), as a means of encouraging trials of combinations of novel drugs developed either within one company or between different companies. Given that few legislative days are left this year (and Congress is expected only to convene for a post-election "lame duck" session), the current bill could serve as the springboard for debate on the topic when the new Congress convenes.

The bill would grant six-month extension of market exclusivity and expedited priority review to qualifying therapies with a "significant drug combination designation." This term is defined as a combination of two or more drugs – including biologics – that are not approved and also meet the following criteria:

- When used in combination, the drugs offer the potential to significantly advance treatment for a serious or life-threatening disease.
- In combination, meet the criteria for co-development of drug combinations, as specified in FDA's guidance document: "Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination" or a successor document.

Released in December 2010, FDA's draft guidance on co-development establishes a regulatory framework for testing novel drugs regulated by the Center for Drug Evaluation and Research in combination, with the caveat that the pathway applies only to novel drugs for "serious" diseases (["FDA Issues Co-Development Guidance, But Only For Products Treating "Serious" Diseases" — "The Pink Sheet" DAILY, Dec. 14, 2010](#)). Vaccines, blood products and gene or cellular therapies were excluded.

According to the new draft legislation, a "significant advance" means that the combination provides treatment of "one or more life-threatening or other serious diseases or conditions for which no therapy exists." Alternatively, if one or more therapies are available, the drug combination must be demonstrated to be superior to available treatment, or else minimize development of drug resistance.

The main incentive for industry in the bill is the six months of extra exclusivity, explained Tim Turnham, executive director of the Melanoma Research Foundation, which pitched the concept to Bilbray's office. Bilbray's daughter was diagnosed with Stage 3 melanoma at the age of 24. Bilbray and Maloney also

introduced the Melanoma Research Act of 2012, which would direct taxes from indoor tanning services to support skin cancer research at the National Institutes of Health.

However, the new bill is not just for melanoma – it is targeted broadly at life-threatening diseases.

A Carrot For Risky Combo Trials

Clinical demand is great for combination therapies, particularly in oncology, but there have been many hurdles for development, including a lack of regulatory clarity for development as well as intellectual property and competitive issues that dissuade companies from collaborating. Furthermore, testing two novel drugs together could make it harder to tease out the cause of toxicities, creating liability as well as development risk.

“This bill is really useful. It provides a carrot ... a financial incentive that would offset some of the financial risk [companies] perceive might be associated with those studies,” Turnham said in an interview.

In addition to extra marketing exclusivity, the bill also offers significant drug combinations priority review and fast track designation. Furthermore, it calls for the creation of an interagency “co-development task force,” which would be required to report to Congress within a year about the challenges in developing combination therapies and propose policy changes to support these programs.

The bill is similar in some ways to the Generating Incentives for Antibiotics Now provisions of the FDA Safety and Innovation Act. GAIN offers an additional five years of marketing exclusivity, plus priority review and fast track incentives for drugs targeted at serious or life-threatening infections. FDA recently announced the creation of a new Antibacterial Drug Development Task Force to help implement the GAIN provisions and incentivize development of new drugs (["FDA Antibiotic Task Force Developing Standards To Help Products GAIN Traction" — "The Pink Sheet" DAILY, Sep. 24, 2012](#)). Some companies say that GAIN will mainly benefit drugs with short patent life and therefore is of limited value, though they appreciate the imperative for FDA to change the way it regulates to encourage development of novel antibiotics (["View From ICAAC: How Higher Prices Can Help Save Antibiotic R&D" — "The Pink Sheet," Sep. 17, 2012](#)).

Bilbray’s office said that the combination therapy initiative was not modeled after GAIN, but rather on earlier legislation for incentivizing development of drugs for HIV/AIDS. Turnham also pointed to the precedent of legislation offering a six-month period of marketing exclusivity in exchange for testing of drugs in children.

Is Six Months Enough?

Considering how complicated co-development is, it remains to be seen whether the incentives proposed in the new bill would be effective, in combination with FDA’s draft guidance.

[Merck & Co. Inc.](#) and [AstraZeneca PLC](#) have been pioneers in the co-development of combinations of investigational drugs, with an announcement in 2009 of plans to test Merck’s AKT inhibitor MK-2206 with AstraZeneca’s MEK inhibitor AZD6244 in a Phase I lung cancer study (["In A First, Merck And AstraZeneca Team Up For Oncology Study" — "The Pink Sheet" DAILY, Jun. 1, 2009](#)). Merck says it remains committed to the investigational co-development research, with four trials of this combination ongoing in colon cancer, melanoma, advanced solid tumors and lung cancer.

But this partnership was then, and remains now, a rarity in the industry.

The melanoma field has been dramatically changed in recent years by the development and approval of two new drugs, [Bristol-Myers Squibb Co.](#)'s *Yervoy* (ipilimumab) and [Roche](#)'s *Zelboraf* (vemurafenib). Though the two have different mechanisms, the potential for the drugs to be used in combination was recognized while the two drugs were in development. But nothing happened until both drugs were approved, and even then it took a long time before they were tested together, Turnham commented (["Bristol/Roche Finally Start Combination Melanoma Trial" — "The Pink Sheet" DAILY, Jun. 2, 2011](#)).

The FDA guidance issued in late 2010 had been a step in the right direction. In comments on the draft, industry requested far greater flexibility in terms of the types of drugs that could be tested in combination, including drugs that are approved but are investigational in terms of new indications or new combinations (["Drug Developers Ask For Flexible Combinations In Co-Development Regulation" — "The Pink Sheet," Feb. 21, 2011](#)). Companies also felt that FDA's suggestion that a combination show greater than additive efficacy compared to the individual agents alone set too high a bar.

At a meeting organized by the nonprofit Friends of Cancer Research in May 2011, CDER Director Janet Woodcock described the guidance as "a start" but "really just a first step" (["Beyond The Guidance: The Business Of Co-Development Combinations" — *Pharmaceutical Approvals Monthly*, May 2011](#)).

While FDA was willing to be "very forthcoming" in presenting different scenarios on their regulatory approach, many other challenges remained, reflected Jeff Allen, executive director of Friends of Cancer Research, in an interview about the Bilbray/Maloney bill. "This challenge wasn't FDA's alone. The clarity around the regulatory path was just one hurdle in the way of seeing more multidrug combinations," Allen said.

On top of the scientific challenge of finding the right targets and combinations, companies are not adept at overcoming logistical barriers to working together, such as sharing intellectual property and revenue streams.

"There is reluctance to lose control of these agents," Allen said. "When you start doing research that involves multiple companies, you lose a bit of control over what the future development paradigm is for your product. And with such a giant investment required to move drugs forward, there is a financial challenge."

The question is whether a financial reward is great enough to spur some companies to pioneer solutions to these issues and hopefully create a model other companies can follow in the future, he added.

Even within one company, challenges remain for co-development. Pharmas may be acquiring later-stage targeted drugs at considerable expense, and combining valuable assets in a combination study creates a risk for additive toxicity. It might be difficult to attribute side effects to the components and toxicity for the combination could taint the individual drugs as monotherapies, Allen said.

Allen declined to comment specifically on the value of the six-month incentive in the new bill, but said that generally speaking, there is "mixed opinion" about lengthening exclusivity to achieve this aim. One concern is the price to be paid for longer exclusivity, particularly for extremely expensive cancer drugs, he said.

Turnham said that anecdotal feedback from pharma companies suggests six months of additional marketing exclusivity would spur development. Commenting on prospects for the bill's passage in an election season, Turnham said that "there's no telling what can or will happen," but those who work in melanoma research and clinical care agree that combination therapies offer the very best promise for patients.

“This is now incumbent on us as a patient advocacy group to inform patients about the significance of this legislation and give them tools by which they can reach out to their legislators and encourage them to get behind this bill,” Turnham said.

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