FDA still working on 'breakthroughs'

By Robert F. Church and Bert Lao

A significant new opportunity exists for drug and biotechnology companies hoping to bring innovative new therapies to market. The U.S. Food and Drug Administration's new "breakthrough therapy" program offers a number of benefits designed to expedite product review and bring promising treatments to market more quickly. This program was enacted in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA).

The breakthrough therapy program includes all of the benefits of FDA's existing "fast track" program, such as a rolling review process that allows a sponsor to submit individual parts of a product application for FDA review as they become available, instead of waiting to assemble a complete application. A breakthrough therapy designation also allows a sponsor to receive input from FDA on structuring clinical trials so as to promote efficient development of the product.

To date, the breakthrough therapy program has proven to be popular with industry. Thus far in FDA's 2013 fiscal year, drug manufacturers have submitted 77 requests for breakthrough therapy designation to FDA's Center for Drug Evaluation and Research (CDER). Of those 77 requests, CDER has granted 27 and denied 25 (the remaining requests have not yet been acted on).

Much remains unknown, however, about the decision-making process FDA employs in deciding whether to grant breakthrough therapy designation to a product. The legal standard for designation is specified at Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by FDASIA. Section 506(a) states that a product will receive a breakthrough therapy designation if it "is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate

ing fast track, accelerated approval and priority review programs. To be sure, the language in the statute requiring a breakthrough therapy to "treat a serious or life-threatening disease or condition" is a prerequisite similar to FDA's established expedited review programs. And, as noted above, many of the benefits of a breakthrough therapy designation are shared with FDA's fast track program. What is the rationale and purpose, then, of the breakthrough therapy pathway?

Presumably, the distinguishing feature of the breakthrough therapy program is the requirement to "demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints." Comments from FDA have suggested that this is meant to be a rigorous standard. John Jenkins, FDA's director of the Office of New Drugs, has stated that a breakthrough therapy designation is a "high bar," and described the information necessary to support a breakthrough designation as follows: "This is a result that's so impressive, so unexpected, and has such a dramatic impact on the treatment of patients with that disease, that both FDA and the sponsor, everyone should put all the resources into discussing how to expedite that drug, if ... that promise holds up through the further drug development program." Derrick Gingery, "Industry Wants a Breakthrough Therapy, Even Without All the Standards," The Pink Sheet (Oct. 29, 2012).

In light of these comments, it is somewhat surprising that FDA has granted 27 breakthrough therapy designations as of this fiscal year to date. To put this number in perspective, one report suggests that FDA was expecting to grant no more than three or four breakthrough therapies a year, and has questioned whether the agency will have the resources to support this many designations. Kate Rawson, "FDA's 'Breakthrough' Exceeds Expectations; Will It Break the Bank?," The RPM Report (Aug. 9, 2013).

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review documents are currently available that might shed light on FDA's breakthrough therapy designation process.

Although no drug review documents from breakthrough therapy products are currently available, FDA has recently issued a draft track program. The key requirement for fast track designation is to "demonstrate the potential for unmet medical need." The draft guidance presents examples of approaches for fast track designation that are conceptually similar to the examples of approaches for demon-

There are differences in the type of data that FDA will accept for these designations, however. While FDA will accept both nonclinical and clinical data in support of fast track designation, only clinical data for a clinically significant endpoint will be considered for breakthrough therapy designation.

Ultimately, it may just be too early for FDA to have adopted a consistent, well-defined approach to breakthrough therapy designation. As CDER director Janet Woodcock has stated, "Right now it's 'you know it when you see it' ... Of course that isn't very sustainable over the long term, but I think we have to get a number of experiences under our belt before we

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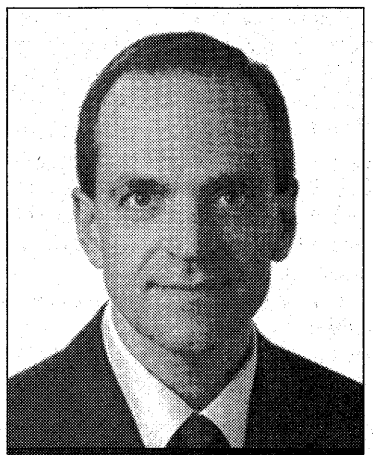

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The breakthrough therapy program includes all of the benefits of FDA's existing "fast track" program, such as a rolling review process that allows a sponsor to submit individual parts of a product application for FDA review as they become available, instead of waiting to assemble a complete application. A breakthrough therapy designation also allows a sponsor to receive input from FDA on structuring clinical trials so as to promote efficient development of the product.

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Much remains unknown, however, about the decision-making process FDA employs in deciding whether to grant breakthrough therapy designation to a product. The legal standard for designation is specified at Section 506(a) of the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by FDASIA. Section 506(a) states that a product will receive a breakthrough therapy designation if it "is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints." Sponsors may submit a request for breakthrough therapy designation beginning with the submission of an investigational new drug application and any time afterwards. FDA is required by law to respond to a sponsor's request within 60 days.

The breakthrough therapy program is not the first expedited review pathway that FDA has made available. Indeed, the breakthrough therapy program shares many similarities with FDA's existing fast track program. The key requirement for fast track designation is to "demonstrate the potential for unmet medical need." The draft guidance presents examples of approaches for fast track designation that are conceptually similar to the examples of approaches for demonstrating "substantial improvement" for breakthrough therapy designation. For instance, the draft guidance suggests that showing superiority over existing treatment, as well as showing effectiveness where no available therapy exists, are valid approaches for demonstrating both unmet medical need and substantial improvement.

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What accounts for this many breakthrough therapy designations? It may simply be, as observers have suggested, that the higher-than-expected number of designations is a reflection of new advances in drug research leading to a greater number of promising products in development. Without a direct window into FDA's decision-making process, however, it is difficult to say with any certainty the reasons driving FDA's approvals of breakthrough therapy designations. When FDA approves a drug, it makes publicly available a set of documents that serve as a record of FDA's review process. But because no products with a breakthrough therapy designation have yet been approved, no such review documents are currently available that might shed light on FDA's breakthrough therapy designation process.

Although no drug review documents from breakthrough therapy products are currently available, FDA has recently issued a draft guidance for industry titled "Expedited Programs for Serious Conditions — Drugs and Biologics," which provides examples of approaches that may be used to qualify for each of FDA's expedited review programs. But these examples still suggest a broad similarity between the breakthrough therapy program and FDA's fast

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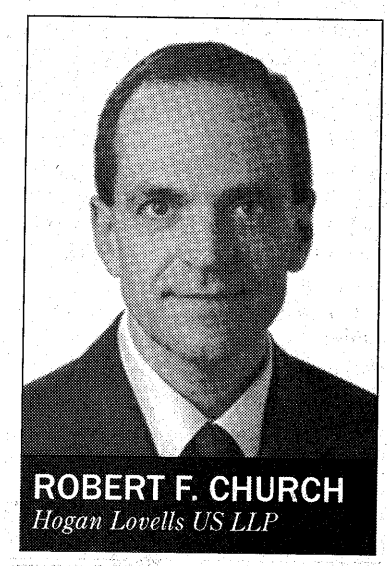

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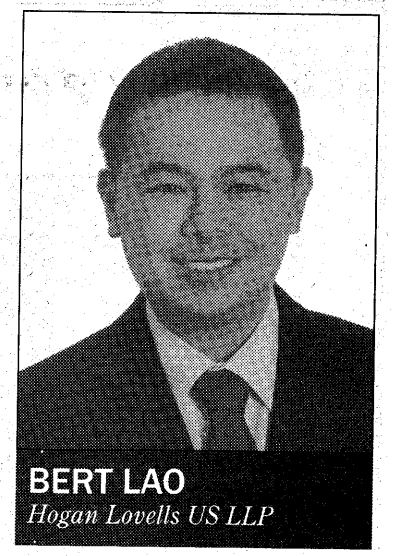

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