



July 2008, Vol. 3, No. 12

## Treat and Trade: The New Priority Review Voucher Market

*Starting in September, pharmaceutical companies will have the opportunity to buy the right to a faster FDA review. If it works, the priority review voucher program could revolutionize development of drugs for neglected diseases, while increasing the value of more traditional commercial products in the US. But sponsors are wary that the vouchers will pay off.*

### Buyer beware.

That is the consensus opinion for biopharmaceutical companies considering the opportunity to buy their way to a faster review by the Food & Drug Administration. Think of the “cap-and-trade” model for CO<sub>2</sub> emissions, only instead of buying the right to exceed limits on greenhouse gas emissions, sponsors would be buying the right to a “priority” designation for their new drug applications, meaning—at least in theory—the chance to enter the market at least four months earlier than they otherwise would.

Starting at the end of September, FDA will begin issuing priority review vouchers under a new incentive program created by the FDA Amendments Act of 2007. The program will reward sponsors of drugs to treat “neglected tropical diseases” by giving them the right to receive a priority designation on any future new drug application—that is, the right to a complete review by the agency within six months, rather than the 10-month standard review timeline. (See [“Antibiotic Assistance,” The RPM Report, June 2007.](#))

It is possible that a Big Pharma company could take advantage of the new program directly—by developing, say, an anti-protozoal medicine for donation to the developing world and then using the voucher on an antidiabetic medication that would not normally qualify for priority status.

However, it is likely to be more common that the priority review vouchers will be claimed



By [Michael McCaughan](#)

### Related Articles

[Playing the Priority Review Market: The Rules for Buyers and Sellers](#)

["Case-by-Case:" How One Company Assesses the Priority Voucher Program](#)

[FDA's Priorities for Priority Review Vouchers](#)

[Cashing in on the Voucher Market: Two Small Cap Biotechs Bid for Attention](#)

by non-traditional sponsors—including non-profits, patient organizations or start-ups—who will then use the voucher as a fund-raising vehicle by auctioning it off to the highest bidder.

If it works, the program could create a new market that, in effect, sets a price on a faster FDA review. Call it “treat-and-trade”: a new type of security that promotes massive global public health advances while allowing sponsors to capitalize on faster commercial launches in the US.

But that is a long way off. The first vouchers have not yet been issued. FDA has yet to define some important details of how the program will work. And, most important, no one can say for sure whether a priority review voucher will really mean a faster time to market. If the vouchers can’t translate into a faster review from FDA, then they will have little or no value to other drug sponsors.

Still, everyone does agree on one thing: the prospect of a faster FDA review is too valuable to ignore. And, in the coming months, every drug development company will have the chance to buy a priority review voucher.

The question is, how much is a priority review worth?

The three economics and business professors from Duke University who initially proposed the voucher incentive suggest its value could be as high as \$600 million. FDA Orphan Products Development Office Director Tim Cote—one of the agency officials charged with implementing the new program—says he has heard “conjectures” that the value could be between \$50 million and \$300 million.

Business development and regulatory affairs execs in Big Pharma companies say they are thinking of a lower figure.

It’s not that they doubt the value of a priority review (though they think that \$600 million seems high for any but the biggest potential markets). Rather, they want to see that the vouchers actually work first.

Across industry there is doubt about whether—even with the best intentions—FDA will actually deliver a faster review for a product covered by a voucher.

As **Wyeth** SVP-corporate business development Thomas Hofstaetter puts it: “I would need to see the first example before I really believe it.”

### FDA Must Prove Voucher’s Value

Hofstaetter is not alone in that sentiment.

Industry executives raise two critical questions about the potential for the voucher program to pay off:

(1) Will FDA actually give a priority review to an application that would not otherwise qualify?

(2) Even with the best intentions, can FDA deliver a faster review given current resource issues?

“There is no way having a priority review slot would make a non-priority product into a priority one,” says Bruce Burlington, the former head of global regulatory affairs at Wyeth and a 20-year FDA veteran. The agency will make a “good faith effort,” Burlington says, but “a priority product is directed at what FDA believes is an important unmet medical need. That inevitably influences their risk tolerance in the product’s favor when compared to the tolerance for a well-met need. Buying a priority slot wouldn’t change that.”

Another former FDA official, Scott Gottlieb, agrees.

“Internally the FDA doesn’t like this program,” the former deputy commissioner says. “While I’m sure they will dutifully implement it as prescribed by Congress, I suspect they will not give it full credence and are unlikely to push to review drugs in priority time frames when the underlying product does have substantial importance and wouldn’t meet any of the criteria of a priority product, save for the voucher.”

“You may well see a number of those voucher-based priority reviews get extended,” Gottlieb predicts, “and I suspect industry will get the message rather quickly.”

That is not how one of the officials charged with making the program work sees it. “I have no doubt that this FDAAA provision will be enacted exactly as provided for by statute,” says FDA’s Cote. “The voucher is law and law is taken very, very seriously at FDA.”

However, some interested parties say FDA officials have been candid in recent meetings in acknowledging that there is discomfort with the idea of defining priority review status based on a non-scientific issue.

And regulatory affairs executives in several companies say their advice to senior management is not to assume that a priority review voucher will necessarily mean as much as a priority review designation does now.

### Concerns about Resources

Then there is the question of whether, even if FDA wants to make the program work, it will be able to deliver a palpably faster review given the resource constraints and other pressures on the agency. (See “[Straight Talk From FDA](#),” *The RPM Report*, November 2007.)

The bottom line, Burlington says, is whether a voucher “would really translate into shaving four months off the total review time to approval. I don’t know, but, given the way FDA is

staffed today, I really doubt you would get the full time savings.”

One Big Pharma regulatory affairs executive highlights that concern. It is “difficult to quantify the value” of a priority review voucher in part “because we see timeline slippages in many priority reviews for a variety of reasons” already.

In theory, those resource questions will be addressed by a special user fee that the voucher holder will pay; the fee will be calculated to cover the cost of additional resources needed to speed up the review. That is one of the critical elements of the program still to be defined by FDA. (See [“FDA’s Priorities for Priority Review Voucher.”](#))

However, **Merck & Co. Inc.** VP-public policy Ian Spatz points out, the supplemental user fee approach is untested—and may be difficult for the agency to implement effectively. Spatz notes that FDA stresses the importance of stable and predictable funding to allow it to hire and retain reviewers to shoulder the workload.

For instance, the aborted direct-to-consumer advertising fee program was designed to ensure that FDA had both a predictable baseline level of funding from year to year, as well as a built in reserve fund to ensure that new reviewers would not have to be let go because of temporary dips in fees. (See [“DTC User Fees Shot Down,”](#) *The RPM Report, January 2008.*)

The priority voucher fee program will attempt to address that concern by requiring sponsors to give FDA one-year’s notice before submitting an application that will use a voucher. That notice is a binding commitment to pay the fee—even if the sponsor ends up not using the voucher (or even submitting the application).

Still, even with a year’s notice, it may be difficult for FDA to use the new fees effectively. If the agency receives a voucher fee for an antidiabetic drug, for example, it can’t necessarily use that to hire another reviewer in that specialty: there is no guarantee that the division would receive adequate funds to support the reviewer in subsequent years. And even if there was, 12 months isn’t enough time to recruit, hire and train a reviewer anyway. (See [“Reinforcements at Last,”](#) *The RPM Report, June 2008.*)

### **Killing Bugs and Worms**

There are sound reasons for industry to be concerned about FDA’s ability to deliver a priority review in exchange for a voucher. But there is also clearly strong interest within FDA in encouraging the development of drugs to treat neglected diseases.

In Cote, FDA has a passionate advocate for the program. Cote discussed vouchers as part of a presentation to an Institute of Medicine workshop June 23 on business models to support drug development for rare and neglected diseases. The voucher program, he says, could “change everything” in the field of tropical disease research.

Cote started as head of the Orphan Products Office at the time FDAAA was enacted. Since then, he has made it a priority to get Big Pharma more engaged in developing drugs for rare diseases covered by the 25-year old Orphan Drug Act. (See "[New Business Models for Personalized Medicine](#)," *The IN VIVO Blog*, June 25, 2008.)

He is also excited about the potential for the tropical disease voucher program to, as he puts it, encourage industry to "kill more bugs and worms," and clearly sees potential payoffs in public perception of the industry.

And he sees a big potential in the market for vouchers.

"The important thing about this priority review voucher is that it is transferable, so you can sell it, and another company—say a Big Pharma company—could come up and buy that priority review voucher and apply it to any other drug," Cote said. "Let's say the Big Pharma company has a possible blockbuster or a new erectile dysfunction drug or something that they are really excited about and they want to get it out really fast. This priority review voucher will get it out really fast."

Cote cited estimates ranging from \$50 million to \$300 million as the value of a voucher. However, he cheerfully admits, "there are lots of people making such conjectures, so they vary widely." The ones he cites are "the ones I have heard and so, as noted, they are unabashed hearsay."

So, Cote acknowledges, "how much this priority review voucher is worth is the subject of some conjecture and it really won't be decided until they hit the market."

### Clear Indications of Interest

All reservations aside, it is clear that Big Pharma companies are intrigued by the potential to buy a faster review.

"We are pretty confident that, if we complied with the legislative language, FDA would provide a priority review as required under the law," **Pfizer Inc.** Global R&D VP-science policy and public affairs John Swen says. "Whether or not that led to an accelerated approval is harder to assess."

"Given the novelty of this approach, it will take some time to see how it actually works," Swen says. Still, "our overall assessment is that the voucher could have significant value—enough to carefully consider programs in this area."

*Exhibit 1*

**Putting a Price on Priority Status:**  
*Metrics for setting the market for priority review vouchers*

<b>\$2.5 Billion</b>	Four months of Lipitor sales in the US
<b>\$775 Million</b>	Increase in Lilly market cap due to Priority Review designation for <i>Effient</i>
<b>\$750 Million</b>	Decline in Lilly market cap due to extension of <i>Effient</i> review
<b>\$50-\$300 Million</b>	Estimated value of voucher, according to industry officials cited by FDA
<b>\$100-\$200 Million</b>	Estimated value of voucher, according to industry sources interviewed by <i>The RPM Report</i>

SOURCE: *The RPM Report*

The recent review trends out of FDA suggest that a priority review is indeed an extremely valuable asset—at least when it is awarded based on the agency’s initial assessment of the importance of an application. (See [“FDA’s Outlook on the Drug Approval Drought,”](#) *The RPM Report*, February 2008.)

The average approval time for applications given priority status is much shorter—6.5 months versus 16.8 months in 2007—as is the chance that the application will be approved at all.

But at a time when FDA is missing user fee deadlines under the strain of balancing all the new safety priorities it faces, it is an open question whether those figures still apply—even for “true” priority review products that would fall outside the voucher program. (See [“The New User Fee Rules,”](#) *The RPM Report*, March 2008.)

One recent high-profile case illustrates that point: Lilly’s platelet inhibitor prasugrel (*Effient*) was granted priority review status in February, pleasantly surprising investors who saw the decision as a vote of confidence in a quick approval. (See [“Prasugrel and Wall Street: Lilly Tries to Stop the Bleeding,”](#) *The RPM Report*, January 2008.) However, as the six-month review deadline approached, Lilly announced that the deadline has been extended by three months.

Still, executives in drug development and regulatory affairs generally believe that priority review status translates into about a six-month head start into the market.

And the potential for a faster review is simply too valuable to ignore.

“It is worth real money,” says Merck’s Spatz.

Spatz wrote to *Health Affairs* in response to an article initially proposing the voucher model to suggest that a priority review might not be the most effective incentive to encourage development. Spatz suggested that patent extensions would be more likely to generate the desired R&D—since the reward is more certain.

He hasn’t changed his mind about that, but he also stresses that the priority review voucher has at least some potential value, and that it is impossible for companies to ignore the opportunity.

That seems to be the consensus of industry executives interviewed by *The RPM Report*.

Several companies say they plan to consider acquiring vouchers on a “case-by-case” basis. And the key will be using the voucher for the right kind of application, they say.

Former deputy commissioner Gottlieb suggests that “sponsors may be smart in how they deploy this program and use the vouchers around drugs that don’t qualify for priority review but meet many of its important criteria nonetheless, making it more likely FDA will respect the timeframe attached to the voucher.”

The key, in Gottlieb’s view, is perception. That is—despite Cote’s example at IoM—don’t try to use a voucher for a product like an ED therapy where FDA will be especially vulnerable if the approval backfires.

“The agency may well steer sponsors toward using the vouchers in situations that don’t create perception problems and that fulfill more public health needs,” Gottlieb says.

One regulatory affairs exec at a mid-size pharma company says he would want to first discuss the potential of using a voucher with the responsible review division, making sure that officials believe the use would be appropriate—and that they have the capacity to make a priority review meaningful.

The executive also stresses the importance of considering “the robustness of the data in the application so that a priority review would actually result in an approval rather than ‘approvable’ action.”

“It depends on the division and the data,” he says.

Like Burlington, the exec recognizes the importance of employing the voucher in a setting where a safety issue is unlikely to trip up the review.

However, that may be easier said than done: the law requires sponsors to provide FDA with 365 days notice before filing an application that will use a voucher. That notice in turn commits the sponsor to paying a special user fee to support the cost of the priority review. (See [“Playing the Priority Review Market.”](#))

In other words, sponsors will need to decide whether to redeem a voucher before they have completely analyzed their Phase III data package.

### How Much to Pay

Valuation of a priority review voucher itself does not seem to be much of a stumbling block—assuming you accept the premise that the voucher will translate into a quicker entry to market.

It is a classic “what is an extra day in the market worth” analysis, says **Campbell Alliance’s** Ben Bonifant. If you think a drug will generate \$1 billion a year at peak with a 35% profit margin, calculating the value of an earlier entry is simple, he says.

That is the kind of math underpinning the estimates by the three Duke authors who proposed the program in the first place: Henry Grabowski, David Ridley, and Jeffrey Moe. In the original *Health Affairs* article, they calculated a value of about \$300 million for a voucher used on a “blockbuster” drug (\$1 billion in sales after five years on the market), based on the assumption that time to market for a priority review product is about one year faster.

In a paper recently presented at a Stanford University conference on pharmaceuticals in the Asia Pacific, the authors updated that analysis to include the potential value of a longer effective patent life on the product and for a potential “early mover” advantage captured by obtaining a priority review. That analysis suggests a value as high as \$650 million for a voucher, they estimate.

Few people dispute those estimates. Where it gets complicated is in considering the assumptions about how much sooner a product will get to market using a voucher (as opposed to historical estimates based on FDA designated priority status).

Those issues pose challenges, Bonifant says, but “they are not intractable.” The uncertainty surrounding FDA’s willingness to afford true priority status to a voucher application means that sponsors will “heavily discount” the value of the voucher, he says.

Since the voucher will be used for projects that are not otherwise obvious priority review candidates, Bonifant notes, that suggests they will be most valuable for compounds entering “a competitive market with complex trial designs that would take a long time anyway.” In other words, sponsors will want to use the vouchers in precisely the markets where FDA is most likely to complete a review by asking for more data.

Still, Bonifant points out, a voucher will pay off if it delivers a faster review—even if it ultimately means a two-year approval cycle instead of two-and-a-half year cycle.

The requirement to notify FDA one year before filing means that sponsors also need to

discount the risk of a late Phase III failure. That calculation, Bonifant notes, is more routine than the discount due to uncertainty over FDA's ability to deliver a priority review.

Sponsors will also have to factor in the cost of the user fee program to support the voucher, since that will increase the net cost of the faster review. Again, that calculation is relatively straightforward, once FDA announces the fee amount.

Last but not least, the theoretical value of the priority review voucher would also depend on the scarcity or abundance of the vouchers, Bonifant notes. If there are multiple sponsors taking advantage of the tropical disease incentive program with vouchers to sell, buyers may be able to buy at prices well below the amount they would pay if there is only one voucher available for a make-or-break NDA.

For instance, Bonifant says, if there are 10 vouchers available, a sponsor should look to pay no more than the value of the voucher for the project that would be tenth on the list of those most likely to benefit. They should seek to pay no more than the company "with the least need."

Multiple vouchers might also make it less likely that FDA could meet the demands of more simultaneous priority reviews, further reducing their real value.

### Finding the Magic Number

How does that turn out using real numbers? The high end would be defined by *Lipitor*, which generates about \$2.5 billion in sales every four months. (*See Exhibit 1.*) Of course, even the most optimistic sponsor is unlikely to view that as a realistic peak sales estimate for their Phase III project.

On the other hand, most in industry believe a priority review translates into at least a six-month head start on the market.

The consensus of executives interviewed by *The RPM Report* is that a realistic value for a priority review might be in the \$100-\$200 million range.

Here is how Wyeth's Hofstaetter would do the math: "If you assume that a priority review adds about six months to the product exclusivity, it is not difficult to calculate the value which, of course, would depend on the expected peak sales/brand profit. If sales at the time of losing exclusivity were \$1 billion and the net profit margin, say, \$600 million, six months at that time would be \$300 million. But this would then have to be discounted to get a net present value which would have to be adjusted for the risk that the product might not reach the assumed potential and one would also not want to transfer the full value to the 'seller,' so the real value of such a voucher would be much lower."

"In other words," Hofstaetter said, the FDA's proposed range of \$50-\$300 million "is not

unrealistic, but the high end would require a pretty large product potential of several billion.”

Another Big Pharma company offered its analysis (on condition that the company not be identified). That analysis, like Wyeth’s, suggests that published models valuing a priority review at \$300 million have to be adjusted for “additional risks associated with the conditions of this specific incentive and current trends in drug development.” (See “[\*Case-by-Case: How One Company Assesses the Priority Voucher Program.\*](#)”)

### A Sellers Market at First

Once a market emerges, of course, valuation will be a bit simpler—sponsors are more likely to be quoted a market price, that they can accept or reject without negotiating terms tied to their own specific needs.

It is difficult to predict how many vouchers will be available for sale or when. Vouchers are to be issued upon FDA approval of a qualifying application, and the law stipulates that FDA wait one year after enactment before issuing the first voucher. So the earliest possible date for a voucher to become available is September 27.

But there are already indications of interest from start-up companies and non-profits in taking advantage of the program.

The highest profile endorsement came from Bill Gates, the former Microsoft CEO turned global health philanthropist/entrepreneur, who cited the new incentive from the podium at Davos. Other not-for-profit organizations—like **Institute for One World Health**—are also interested in the potential for the voucher to support their philanthropic drug development initiatives. (See *Exhibit 2.*)

*Exhibit 2***THE SELLERS***A Sampling of Companies That May Earn Priority Review Vouchers*

Sponsor	Project (indication)	Status
One World Health	Paromomycin (leishmaniasis)	Clinical Trials Complete
ViroQuest Pharmaceuticals	Lenocta (leishmaniasis)	NDA planned for 2008
Drugs for Neglected Diseases initiative	Multiple compounds (sleeping sickness, Chagas, leishmaniasis)	Preclinical to Phase III
OFLOTUB	Gatifloxacin (TB)	Phase III
Acambis	Dengue Fever vaccine	Phase III
Intercell	Malaria, TB vaccines	Clinical Trials
Avant Immunotherapeutics	Cholera vaccine	Phase II
Aeras	TB vaccine	Phase II
Emergent Biosolutions	Typhoid vaccine	Phase II
Sanaria	Malaria vaccine	IND stage
Upstream Biosciences	Compounds for malaria, leishmaniasis, sleeping sickness	Preclinical
Afya World Medicines/Infectious Disease Research Institute	TB treatments	Discovery

SOURCE: *The RPM Report*

On the for-profit side, some biotech companies are talking up the potential value of vouchers in a quest to attract investors. One very small-cap company, **VioQuest Pharmaceuticals Inc.**, says it could have a voucher to sell early next year. (See "[Cashing in on the Voucher Market: Two Small Cap Biotechs Bid for Attention.](#)")

Duke's Moe points out that the first companies to receive vouchers will get them essentially by serendipity, since the incentive program didn't exist when they began research on the drugs that they are now bringing to FDA. But they will be the key programs in defining the success of the voucher of as an incentive, because everyone will be watching to see how those first reviews go.

That may suggest that the first vouchers will be used by companies that generate them internally. For example, **Sanofi-Aventis** has a dengue vaccine in development, in partnership with **Acambis PLC**, which means that there would be essentially no cost to

the company of obtaining a voucher to try out on another brand. Other Big Pharma companies with active projects in diseases covered by the voucher program include **GlaxoSmithKline PLC** and **Novartis AG**.

Still, the rest of industry may have to wait a year or two to find out how the voucher program plays out.

In the meantime, VioQuest and others are likely to be offering vouchers for sale. Campbell Alliance's Bonifant is sure of one thing: he wouldn't want to be the first one to buy. "I wouldn't buy a voucher without negotiating with a lot of people," he says. If there is just one available, it will—by definition—go to the highest bidder.

Or, as one company's internal analysis puts it, "the ability to buy or sell a voucher earned through this legislative incentive may also enhance the value of a voucher by giving it the potential to be applied to the most valuable late-stage program across the entire biopharmaceutical industry at a given time."

### Putting a Price on FDA Approval

If the first vouchers pay off for sponsors, things will get really interesting. Because then the march begins towards a market in buying and selling the vouchers as an asset.

Duke's Moe says he has already been contacted by entrepreneurs interested in buying and holding vouchers—in effect, they are ready to bet that their value will prove to be higher than drug development execs are willing to pay today.

If a market emerges, Moe stresses, then the incentive value of the voucher is at its peak: investors of all kinds can understand the value of research in tropical diseases, making it easier for non-profits to raise funds to do the research—and, critically, encouraging Big Pharma companies to rethink the potential of entering the market directly.

Once it is clear how much a voucher is worth, it is much easier for pharma companies to justify spending more on internal projects to treat neglected diseases.

But it also makes it much easier for critics of FDA or the pharmaceutical industry to assign an economic value to a speedy review.

One thing the voucher program does, former FDAer Gottlieb observes, is "assign economic values to the review process, unmasking in a market-based fashion how much regulatory shortenings, or for that matter regulatory delays, cost in terms of direct economic value."

Gottlieb argues that is one reason FDA itself doesn't like the program.

"From a perception standpoint, that can put pressure on FDA both ways," he points out, "unmasking the economic costs of regulatory delays while also making the regulatory review process and efforts that make that process more efficient appear to be a direct

economic benefit to sponsors rather than to patients.”

“Once you assign a value to a priority review you have a measure for how much any regulatory shortening, whether it be a day a week or a month, is worth to sponsors. You can rest assured that measure is going to be used by industry critics to try and undermine any attempts at improving the review process and making it more efficient.”

That does not seem to be a big concern in industry. Spatz, for example, sees the issue differently. The voucher program sets a value on the “delta” of the difference between a standard and a priority review. An FDA review itself, he says, is “priceless,” since a medicine has no value to a sponsor without FDA approval.

Indeed, Spatz says, the program could have the opposite effect. If it works, and industry can in fact buy a faster review for a market-driven price, why not just let industry pay that price for any product—voucher or not? After all, if Pfizer ends up paying \$100 million for a priority review voucher—and then a much smaller user fee to cover the cost of the priority review—who loses if Pfizer simply pays \$100 million to FDA for the faster review in the first place?

Those questions, though, are a long way off. First, there has to be a “treat-and-trade” market in voucher incentives. One thing all parties agree on: the new program presents an intriguing business opportunity—one that already has the attention of Big Pharma drug development organizations. It has the potential to deliver major global public health benefits in the form of new medicines for neglected diseases, while simultaneously delivering big commercial returns in the US in the form of earlier market entry.

But first, FDA will have to make the program work—and someone will have to take a chance by buying the right to go first.

*The RPM Report*

Comments? Email the author at [windhover-dc@windhover.com](mailto:windhover-dc@windhover.com)

[Playing the Priority Review Market: The Rules for Buyers and Sellers](#)

["Case-by-Case:" How One Company Assesses the Priority Voucher Program](#)

[FDA's Priorities for Priority Review Vouchers](#)

[Cashing in on the Voucher Market: Two Small Cap Biotechs Bid for Attention](#)

