PDUFA renewal plans include longer reviews and more meetings

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When US Congress considers reauthorising PDUFA, the law that levies fees and sets deadlines on drug applications, it will debate a set of revisions changing drug-review deadlines and, it is hoped, improvements in the interaction between the FDA staff and pharma companies.

These are the proposals contained in an FDA-industry agreement framework released yesterday. The anticipated outcome will be more first-cycle approvals, but at a cost: the increased volume of communication between regulators and sponsors may extend the approval process by as much as four months compared with today, and result in more drug companies withdrawing their applications before decisions, observers say.

Communication

First enacted in 1992, the Prescription Drug User Fee Act expires every five years, requiring Congress to periodically reauthorise the law that levies the fees that support more than half of the FDA’s drug review costs. The last renewal, in 2007, was the fourth; one of its major accomplishments was to codify the risk evaluation and management strategies (REMS) that have become a cornerstone of post-approval safety planning.

However, it is the increasing importance of those REMS that has led to delayed approvals and a greater frequency of first-cycle rejections, the industry has argued (Vantage Point - PDUFA renewal spurs debate on deadlines and oversight, December 9, 2010).

Indeed, since the implementation of PDUFA IV the share of first cycle approvals has dropped, according to FDA data. However, as highlighted by EP Vantage, approval times in 2010 were the shortest they had been since 2007 and below the 10-year average (FDA approval times continue to shorten, March 11, 2011), whilst 2011 is likely to see more drugs approved than 2010 (Encouraging signs from quality of new drugs approved so far in 2011, August 18, 2011).

The FDA’s post-approval safety arm, which endorse the REMS, has not gotten involved with drug approvals early enough and has not communicated sufficiently with agency drug reviewers, according to industry; thus, pharma lobbyists have been pushing for increased communication with agency staff to prevent unnecessary rejections and approval delays.

The framework published for public review yesterday - which still needs congressional and presidential endorsement - is the product of more than a year of negotiations among pharmaceutical and biotech industry groups, consumers and agency staff. It includes a strong commitment from the agency to increase the number of meetings and other communications with sponsors during the review process.

There is a catch for industry: the review clock will not start until a 60-day pre-review period has been completed, during which time the agency will identify any issues that will arise during its initial examination of a new drug or biologics application, as well as laying out a review timeline that will notify drug companies whether an advisory committee meeting will be necessary. This means priority reviews will be extended to eight months from the date of filing, and normal reviews 12 months.

Fewer surprises

Extending the review period had been hinted at in early drafts of the negotiated framework (PDUFA renewal takes shape with extended FDA reviews, June 1, 2011). The final draft, which Congress is expected to debate next year, fully fleshes out how the agency plans on ensuring fuller communication that will avert the late-cycle surprises that industry argues results in delays and unneeded complete response letters.

For example, the document strongly encourages a pre-submission meeting no less than 60 days before companies plan to forward their application to the agency. As analysts from MF Global write, this meeting has the potential to add another two months to the approval process “given that sponsors may feel they need to
be in effect ready to file at the time of the pre-filing meeting."

The meeting also requires the FDA to write a letter to the sponsors 74 days following submission – in effect, two weeks after the end of the pre-review period and the start of the review clock – to chart the review timeline, planned date for a mid-cycle review and any plans to hold an advisory committee hearing.

A mid-cycle communiqué is also planned, along with a late-cycle meeting that is intended to be at least 12 days before an advisory committee meeting, which also needs to take place three months before the end of a standard review or two months before a priority review.

The late-cycle meeting is a “new milestone” in the review process, the MF Global analysts write, with numerous implications for pharma companies. For example, at this meeting the FDA will likely disclose the bad news sometimes contained in staff documents prepared for adcoms, which drives stock market volatility. It may also spur more application withdrawals, and it will also give pharma executives the new challenge of how to communicate the FDA staff’s message to investors.

There are signs the FDA is already taking steps in this direction - for example, Transcept Pharmaceuticals pre-announced its expectation that sleeping pill Intermezzo would receive a complete response letter following a late-cycle teleconference with agency officials (Intermezzo disappointment another rude awakening for Transcept, July 13, 2011).

With better communications, the expectation is that similar announcements may come more frequently and earlier in the review process to allow for a formal withdrawal. This may result, however, in fewer first-cycle rejections, which should be a welcome change.

The Pharmaceutical Research and Manufacturers of America and Biotechnology Industry Organization have already both endorsed the new framework. Whilst an unpredictable event like a new drug-safety scare could prompt additions to the legislation, it is probable that these proposals will be in the final bill signed into law.