FDA Watch

Approvable Letters in 2007 and the Outlook for 2008

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Even the most casual observer of the pharmaceutical and biotechnology industries will have noticed that in 2007, the U.S. Food and Drug Administration (FDA) issued an overwhelming number of approvable letters and a corresponding underwhelming number of approval letters for new product applications. In fact, according to a recent publication by Sagient Research, the number of approvals fell by 13% from 2006, while the number of approvable letters increased by 40%.

An approvable letter is sometimes also called a Complete Response Letter, and it means that the FDA has cited some conditions that a drug sponsor must attend to before a product will be approved for the market. Sometimes, companies try to spin this as good news, and although it is better than a nonapproval response from the agency, it is still short of an approval. The conditions on which the FDA demands action may be very easily addressed by the sponsoring company, involving such mundane considerations as label changes or data inclusion or even the development of a risk management plan; however, the conditions may also include new data that necessitate new clinical trials—meaning added expense and time before approval and marketing.

There are many implications related to the issuance of so many approvable letters. The current approval environment represents more than an inconvenience to companies and to patients who are awaiting therapies with serious implications for both, as well as for investors in companies, particularly smaller companies that do not yet have a product on the market. Here are just a few of the effects:

• An Erosion of Intellectual Property—When a company files its application with the FDA, its patent has already begun, and the clock is ticking on that patent. The longer the FDA takes to consider and to approve a new compound, the less valuable the compound is when (and if) it is finally approved and enters the marketplace, because there is less time for the drug to have market share and recoup the investment costs represented in its development. That means either (1) the drug will have to be priced more expensively (which is counter to patient and public interest), or (2) the company may not get back as much funding to reinvest into new research and development (again counter to patient and public interest, as well as those of investors).

• Small Companies Particularly Suffer—In 2007, both small and large companies were well represented among those who received approvable letters; however, if a company with no product yet on the market receives an approvable letter for an investigational compound, it can be devastating to the company. Consider that an approval means that a company wants to move to the market quickly, which requires, among other things, a geared up and trained sales force. An approvable letter necessarily means that a company has to either maintain that force without sales to support it or to lay them off. Needless to say, the return for investors is not there either. If the FDA is moving the goal posts on approvability, the standards should be clear so that the impact on companies, employees, and investors can be minimized. Otherwise, startup and innovative companies may find it harder to raise the cash needed to produce tomorrow’s miracles today. It is in the public interest to have policies that encourage America’s innovation in creating new compounds, not to hinder it.

Also according to the same Sagient Research report, the average stock price change that was the result of an approvable letter dropped in 2007 to 12.89% from 21.42% in 2006, which would mean that approvable letters are having less of an impact and that perhaps investors are adjusting to this new paradigm.

• Setbacks to the FDA Modernization Act and Prescription Drug User Fee Act—In the 1990s, with the HIV epidemic whirling out of control and no treatments for people diagnosed with AIDS, there was a tremendous public appetite (and hence policymaker action) to get drugs approved more quickly. Consequently, there was policymaker action in response. Hence, FDA reform in the form of 2 pieces of legislation accomplished just that by shortening approval times and allowing for Fast Track and Accelerated Approvals. Now, however, we have a situation where the public priority is focused on risk aversion and safety issues, not quick access to new treatments. That means that policymaker actions are likely to follow public angst about drug safety with additional FDA reforms that direct and scrutinize agency approval actions. Although that is happening, it is highly likely that the agency will continue to operate in a mode of operations that lends itself to caution over speedy drug access and approval.

In short, there is every reason to believe that the...
pharmaceutical, biotech, and even device industries are operating in a new approval environment, whether or not they realize it. Safety signals anywhere along the clinical trial trail or pop meta-analyses conducted on the class or the specific compound can mean serious complications for approval, when just a few years ago, they would not have been of serious concern.

There is no reason to believe that the situation is going to improve in 2008. The FDA reform that began in 2007 is likely to continue in 2008 with a great deal of oversight scrutiny by Congress. In the past month, more than one letter has left Congress sent to the FDA to inquire about specific drug approvals and potential conflicts of interest among advisory committee members, the proposed behind-the-counter status of drugs, and whether the system for quicker approval of drugs under Fast Track has been misused. Complicating the situation further will be the election cycle, which has now begun in earnest. It will not only provide a platform for some pharmaceutical industry-bashing, it will also be a showcase for the proposal of further reforms, some of which may be designed to slow down the approval process even more in favor of perceived safety enforcement.

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