By Adam Feuerstein

Biotech 101: The Road to FDA Approval

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There are two things that really get biotech stocks moving -- results from phase III clinical studies and approval decisions issued by the Food and Drug Administration. Genentech (DNA:NYSE) , for example, has been red-hot over the last year because the firm has had unprecedented success on both fronts, leading to FDA marketing approvals for three new products: the psoriasis drug Raptiva, the allergy drug Xolair, and most important of all, the cancer drug Avastin.

The FDA's huge influence on biotech stocks is undeniable, but understanding the drug approval process isn't so easy. It shouldn't shock anyone to hear that FDA rules and procedures, like most governmental bureaucracies, aren't necessarily designed to be easily understood. But a solid understanding of the FDA approval process is essential to smart biotech investing. So, this "Biotech 101" column is for investors who are interested in learning the ins and outs of the FDA. (A previous "Biotech 101" column covering the three phases of clinical trials was published in April.)

Posting Positive

When a drug posts positive results from one or more of the pivotal phase III clinical studies, drug and biotech companies seeking to get the drug approved in the U.S. and the right to market and sell it to doctors, file the drug with the FDA.

ImClone Systems (IMCL:Nasdaq) , for example, has had success since the FDA approved its cancer drug Erbitux. On the flip side, Genta (GNTA:Nasdaq) shares have tumbled because the company was forced to withdraw its cancer drug Genasense from the FDA after the agency's advisory committee voted overwhelmingly to recommend against approval.

Filing a drug with the FDA is literally a big job. Genentech's Avastin filing, for instance, was approximately 11 gigabytes in size, which equals 17 CD-ROM discs, or more than 60,000 printed pages.

Avastin is a biologic drug, which means that it's manufactured by genetically altering living cells and growing them in large vats so that they produce the drug (a protein), like miniature living drug factories. In accordance with regulatory policy, when Genentech filed Avastin with the FDA, it submitted a Biologic License Application, or BLA.

Traditional pharmaceutical products -- i.e., pills -- are made from relatively simply chemical ingredients. Approval filings for these drugs are known as New Drug Applications, or NDAs. But while products covered under BLAs and NDAs differ, the steps taken by the FDA to review the two kinds of approval applications largely do not.

Priority Treatment

The time it takes the FDA to review a drug is mandated by the Prescription Drug User Fee Act, or PDUFA, a law first passed in 1992 that allows the FDA to charge drug companies a fee for reviewing their NDA or
BLA. In turn, the FDA uses this money to hire drug reviewers and, in general, speed up the drug review process. (The FDA has never found an acronym it didn't love -- and use frequently.)

The FDA often grants "priority review" status on drugs that address unmet medical needs or life-threatening diseases such as cancer or HIV. Once a company submits a drug under priority review, the FDA has 45 days in which to accept or reject the application for review. (Recall, ImClone got into big trouble, and Sam Waksal ended up in jail for his actions after the FDA refused to accept the company's original Erbitux application, sending ImClone a so-called refuse to file letter.)

Once the FDA accepts a drug application for priority review, the agency has up to six months -- and generally takes it -- to issue an approval decision. The "PDUFA clock" starts on the day the drug application is filed with the FDA. Drug and biotech firms typically issue press releases when drugs are filed, so it's relatively easy for investors to count forward six months from that day to find the date by which the FDA must issue its decision, often referred to as the "PDUFA date."

Last week, the FDA said it granted "priority review" status to Antegren, the multiple sclerosis drug being developed by Biogen Idec (BIIB:Nasdaq) and Elan Pharmaceuticals (ELN:NYSE). The companies submitted Antegren to the FDA on May 25; thus the drug's PDUFA date falls on or around Nov. 25.

The FDA typically uses a "standard review" to handle drugs for non-life-threatening diseases. Here, the FDA will accept or reject a drug application within 60 days from the filing date, and an approval decision is issued in 10 months. The FDA can request additional time to make a decision, if necessary.

Nay or Yea

When the FDA needs help in determining whether a drug should be approved, it may ask for guidance and recommendations from 21 standing drug advisory committees. These advisory panels consist of experts in their respective fields -- practicing doctors, scientists, statisticians, and industry and patient representatives. The FDA's Oncologic Drugs Advisory Committee (also called ODAC), for example, is stocked with cancer authorities and reviews experimental cancer drugs.

The setup of an FDA advisory committee meeting is similar to that of a legal trial, but instead of deciding guilt or innocence, panel members are asked to decide whether a drug is effective and safe enough for approval. During the meeting, the FDA and the drug company both present their respective analyses of the drug's clinical data, which are then discussed and voted on by panel members.

The FDA makes public its internal analyses of a drug's clinical data -- and often its opinion on whether a drug is approvable or not -- one day before the start of an FDA advisory panel meeting. These closely read FDA "briefing documents," which almost always move stocks, can be found here.

The debate among advisory panel members can often be contentious, with opinions swinging wildly from positive to negative and back again. So to lessen stock volatility, shares of all but the largest drug and biotech firms are halted while advisory panels are in session.

Though the FDA is not required by law to follow the recommendation of its advisory panels, historically it has, albeit with some exceptions. That's why drug stocks react strongly, up or down, based on the recommendations that come out of advisory panel meetings.

Stamps of Approval

After the BLA or NDA is filed and an advisory committee, if required, convenes to vote, the final approval decision is left up to the FDA. You'd think this final step would be straightforward, but it's actually pretty labyrinthine.

The FDA can rule in a variety of ways. The simplest FDA action is the approval letter, issued by the FDA when the agency deems a drug safe, effective and ready to be marketed.

Conversely, the FDA can issue a non-approvable letter when the agency concludes that a drug's clinical data or safety data do not warrant approval. This rejection letter of sorts is, of course, bad news and usually precipitates the drug company's plunging stock price.
Investor confusion can be highest, however, when the FDA issues a complete response letter, or likewise, an approvable letter. Simply put, these actions are akin to conditional approvals, meaning that the FDA requires additional information before it can issue a final ruling. The trick for drug companies -- and investors -- is figuring out how much additional information is required and how long it will take to compile and resubmit.

Unfortunately, the FDA doesn't make complete response or approvable letters public, so investors have to rely on a company's explanation and interpretation of these letters to determine whether a final drug approval is imminent or significantly delayed.

Lest you think drug companies always play straight-up and honest with investors, look at what Biopure (BPUR:Nasdaq) did in July 2003. The company received a complete response letter from the FDA regarding its human blood substitute Hemopure. But instead of telling investors that the FDA was asking for new animal and human clinical studies, Biopure management suggested to investors that the FDA had no substantial issues with Hemopure and that approval was right around the corner.

The truth eventually came out, leading to a decimation of Biopure's stock price, the resignation of most of the company's management, including the CEO, and an ongoing Securities and Exchange Commission investigation. Hemopure is nowhere close to being approved.

Sometimes, a complete response letter can be a benign event, especially when drug companies prepare investors for their arrival. MedImmune (MEDI:Nasdaq) received such a letter in January 2003 for its nasal flu vaccine FluMist. The company responded to the five remaining questions posed by the FDA one month later, as it had told investors it would do, and the vaccine was approved in June.

Likewise, Bristol-Myers Squibb (BMY:NYSE) received an approvable letter from the FDA for its schizophrenia drug Abilify in September 2002. The drugmaker quickly resolved the outstanding issues, and the FDA approved the drug in November 2002.

When the FDA's approvable letter comes attached to a request for new clinical trials, the delay can be quite lengthy. The FDA made just such a request for Symlin, a diabetes drug from Amylin Pharmaceuticals (AMLN:Nasdaq) in October 2001. It took almost two years -- until June 2003 -- before Amylin could conduct another clinical trial and resubmit Symlin for approval. In December 2003, the FDA sent Amylin another approvable letter, requesting even more information. To date, Amylin has yet to tell investors when it thinks Symlin will be approved, if ever.

Adam Feuerstein writes regularly for RealMoney.com. In keeping with TSC's editorial policy, he doesn't own or short individual stocks, although he owns stock in TheStreet.com. He also doesn't invest in hedge funds or other private investment partnerships. He invites you to send your feedback to adam.feuerstein@thestreet.com.