What Is Happening to the Pipeline?
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In January 2008, the independent research firm Sagient released data that evidenced a “significant decline” in new drug approvals by the US Food and Drug Administration (FDA). The data showed that in 2007 there was a 13% drop in approvals and a 40% increase in approvable letters. The approval by the FDA of biopharmaceutical products is included in this decline. According to a recent article by Ronald A. Rader, president of the Biotechnology Information Institute, looking at a 10-year span from 1996 to 2005 reveals an average of 16.6 drug approvals by the FDA during each of those 10 years, compared with only 12 and 11 approvals in 2006 and 2007, respectively, according to the Sagient report. The decline from 2006 to 2007 is shown in the Table.

<table>
<thead>
<tr>
<th>Decision</th>
<th>2007 (%)</th>
<th>2006 (%)</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>64</td>
<td>73</td>
<td>-13</td>
</tr>
<tr>
<td>Approval letter</td>
<td>28</td>
<td>20</td>
<td>40</td>
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Approvable letters, or “complete response letters,” indicate a willingness of the FDA to approve an investigational compound, once certain prerequisites are provided or fulfilled by the drug manufacturer. These additional conditions for approval can vary greatly; they may be as simple as changing a label, or as complex, costly, and time-consuming as conducting new clinical trials to better ensure safety or efficacy of the product.

The slowdown in new products in the United States has a broad ripple effect that negatively affects nearly all stakeholders. First and foremost among them are the very bloodline for new products—investors. According to the Sagient research, the average stock price change that was the result of an approvable letter dropped from 21.42% in 2006 to 12.89% in 2007, meaning that approvable letters are having less of an impact than before and that perhaps investors are adjusting to this new drug approval paradigm.

Second, US patients and the marketplace at large are affected. In March 2008, an article published in the Wall Street Journal titled “Overseas Drugs Hit U.S. Regulatory Snags” cited several large companies that have had drugs approved outside the United States but have hit regulatory blockades inside the United States—these include GlaxoSmithKline, Novartis, and sanofi-aventis, the manufacturers of Cervarix, Galvus (vildagliptin), and rimonabant (also known as Acomplia), respectively, which are still not approved in this country. This means that a growing number of products are available for patients in Europe and in other countries but are not available for US patients.

Third, the slowdown is not good for the FDA itself, at a time when its image has become so battered. Although the current environment is one that begs a conservative take on risk, many of the approvable letters have not been based on safety issues, hence the slowdown in approvals is occurring for reasons largely unrelated to safety concerns. But the FDA is supposed to be committed to bringing new drugs to the market through a number of its own initiatives, such as the “critical path initiative.”

The outlook for the future does not promise improvement. The FDA recently announced that the agency may intentionally miss action dates, by which time a decision on approval is due, namely, the Prescription Drug User Fee Act (PDUFA) date. In fact, according to a recent article published online in the RPM Report, the FDA has signaled that because of work burden, the agency will be allowing PDUFA dates to be missed. The RPM Report quotes Dr Jenkins, head of the FDA’s Office of New Drugs, as follows:

“We are faced with the increased workload relat ed to the implementation of FDAAA and FDA’s Safety First/Safe Use initiative. In addition to the resource increases under PDUFA IV, FDA also saw increased appropriations for FY2008 to help meet the growing workload. The new resources will have a significant impact on our workload/staffing balance in the long term, however, in the short term CDER is approximately 550 FTEs below its ceiling for FY08….To that end, I have granted permission to OND division and office directors to make decisions to bring their unit’s workload into better balance with their existing resources. These decisions will be made on a case-by-case basis since the balance is not the same in all divisions or even the same over time in any given division….In the short term our ability to meet PDUFA goals is expected to decrease. In some
cases we may have to cut back on work by declining requests from sponsors for guidance (e.g., meetings, multiple cycle SPA reviews) and in other cases we may decide to go past the PDUFA goal date for review of an application. In cases where we decide to go past the PDUFA goal date the sponsor will be notified by the division management of that plan."

It is difficult to discern from the “increased workload” when the rate of fees that come to the FDA as user fees under PDUFA has increased substantially. In other words, the pharmaceutical industry is being charged more money for fewer outcomes.

Finally, the delay in product approvals resulting from approvable letters or from deadlines missed by the FDA means that once approved, a product has less time on the market to recover research costs and to supply a profit for the investors. The logical consequence is that prices of the product, once approved, will have to be higher over a shorter period of time.

The United States is by far the largest market for pharmaceutical products, and the current situation is not likely to change that. But, according to the European Federation of Pharmaceutical Industries and Associations, the United States represents nearly twice the sales of pharmaceutical products compared with Europe. In addition, between 1990 and 2006, investment in new research in the United States grew 5 times compared with only 2.9 times in Europe. That means that for all the potential market and all the investment there are fewer products. The slowdown in drug approvals by the FDA may address the current environment, but in the long-run it has a negative impact on nearly everyone.

References

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Articles should discuss key issues that can improve the quality and efficiency of our healthcare delivery system in general and of formulary and drug benefit strategies in particular. Types of articles and topics sought include:

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- Drug updates
- Government reports
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  - Cholesterol management
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