By Samantha A. Roberts, Jeff D. Allen, and Ellen V. Sigal

Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe

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ABSTRACT The US Food and Drug Administration is often criticized as inefficient compared to its European counterpart, the European Medicines Agency. This criticism is especially common in the field of oncology, where severely ill patients have few therapeutic options. We conducted a direct drug-to-drug comparison of the two regulatory agencies' approvals of new oncology drugs. We found that contrary to public assertions, the median time for approval for new cancer medicines in the United States was just six months—and that these new anticancer medicines are typically available in the United States before they are in Europe. Our findings reinforce the need for strong financial and public support of the Food and Drug Administration, so that such medicines can continue to be made available speedily to patients in need.

Samantha A. Roberts (sroberts@focr.org) is a science policy analyst at Friends of Cancer Research, in Washington, D.C.

Jeff D. Allen is executive director of Friends of Cancer Research.

Ellen V. Sigal is chairperson and founder of Friends of Cancer Research.

In recent years the scientific understanding of the basic biology of cancer has undergone a major transformation. With the advent of bioinformatics, it is now possible to elucidate the molecular pathways involved in cancer development and to design drugs to specifically target these pathways. Examples of such breakthrough drugs include Herceptin (trastuzumab), which blocks the effects of a protein that transmits growth signals to breast cancer cells,[1] and Gleevec (imatinib mesylate), which inhibits an enzyme that is active in chronic myelogenous leukemia.[2] This new era of scientific discovery has the potential to lead to new anticancer medicines with greater efficacy and reduced toxicity, allowing patients to live longer and healthier lives.

Despite these breakthroughs, some critics argue that given the advances in basic science, we should be able to develop new oncology drugs more quickly than we do.[3] One reason cited for the slower-than-desired pace is a regulatory environment that is not sufficiently equipped with the resources and scientific foundation needed to evaluate new approaches to cancer treatment.[4] Some critics specifically have characterized the Food and Drug Administration (FDA) as slow and inefficient at reviewing drugs in comparison to its European counterpart, the European Medicines Agency (EMA).[5,6] Furthermore, some have claimed that the FDA has become so risk-averse, it is increasingly difficult to obtain approval for effective drugs in the United States.[7]

To examine these claims as they pertain to new anticancer medicines, we analyzed new oncology drug approvals by the FDA and the EMA. We describe our methods and results below.

Study Data And Methods

We compared review times at the FDA and the EMA for new oncology drugs in the period 2003–10. Our data came from the publicly available drug databases on the FDA and EMA websites; they represent only initial approvals, not supplemental applications. In addition, we investigated only active treatment drugs, not drugs for supportive care, such as pain relievers or antinausea medications.

For each new drug in the United States, we collected the date of the first New Drug Application or Biologics License Application submission

to the FDA and the date of final approval. Once the FDA approves a drug, it can be marketed in the United States.

In the European Union, two steps are required before a drug can be marketed. First, the EMA Committee for Medicinal Products for Human Use must issue a positive opinion on the marketing authorization. Next, the European Commission must adopt that opinion. Thus, for each drug we collected the date of the first Marketing Authorization Application submission to the EMA, as well as the dates of the EMA's positive opinion and of marketing authorization.

To evaluate the efficiency of the FDA and EMA review processes, we compared the agencies' review times. To evaluate the delay to market—or the time between a drug's authorization for sale in the United States and its authorization in Europe—we calculated the number of calendar days between the FDA approval date and the European Commission adoption date.

Study Limitations

Our analysis has several limitations. First, as noted above, we considered only initial approvals and not supplemental applications. Therefore, our analysis did not include prominent secondary uses for drugs already on the market. This limitation is addressed in more detail below.

Our analysis also did not compare postapproval decisions in the United States and the European Union. For example, the FDA recently decided to withdraw approval for the use of the drug Avastin in treating breast cancer, when postmarketing trials failed to confirm that it had a clinical benefit for this use. In contrast, the EMA decided to continue to allow Avastin to be marketed in the European Union for the treatment of breast cancer.[8,9] Such postapproval decisions are rare, however.

Another limitation of our study is that we considered only official review times. This does not take into account difficulties that pharmaceutical companies may encounter in communicating with either agency before submitting their study data, or any difficulties in planning or conducting clinical trials of a drug.

However, the field of oncology is one in which the FDA and the EMA have undertaken several initiatives to coordinate their activities, with the goal of speeding the development and entry onto the market of safe, effective new drugs. For example, they have created a program to provide joint scientific advice to pharmaceutical companies.[10] With the help of these initiatives, manufacturers of oncology products are often able to use the same clinical trials to support approval in both the United States and the European Union. Thus, it seems unlikely that manufacturers experience greater difficulties with the FDA than with the EMA at this stage of oncology drug development.

An additional limitation of our study is that we compared approval data for drugs and biologics only, not devices. Examples of devices relevant to oncology include in vitro diagnostics as well as imaging reagents and equipment. A recent report found that in contrast to our analysis of oncology drugs, the FDA is lagging behind the EMA in review and approval of new and innovative devices.[11] Reforms of the US device review process and new initiatives at the FDA, such as the Medical Device Innovation Initiative, are currently under way.[12]

Study Results

We identified thirty-five new oncology drugs that were approved by either the FDA or the EMA in the period 2003–10 (Exhibit 1). All of the drugs that were approved by both regulatory agencies were available to patients in the United States first. There were two reasons for this difference in the timing of approvals. First, we found that pharmaceutical companies typically submit their clinical findings to the FDA prior to submitting them to the EMA. Second, we found that the FDA consistently took less time than the EMA to review a new oncology medicine. We also found that the FDA approved more oncology drugs and biologics in this period than the EMA did.

Of the thirty-five products we investigated, the FDA approved thirty-two. For this subset, the median time between the submission date and the approval date was 182 days, and twenty products were approved within 184 days. Only three of the thirty-two took more than a year to receive approval.

The EMA did not approve nine of the thirty-two products that the FDA approved in this period. Although several of these products were in development in Europe at the time of our study, marketing authorization applications for two—Zolinza,[13] a new drug to treat a type of lymphoma (cutaneous T-cell lymphoma), and Ixempra,[14] for advanced breast cancer—were withdrawn during the EMA review process because of potential safety concerns.

The EMA approved twenty-six of the thirty-five products identified in our analysis. For this subset, the median time between the submission date and the EMA's issuance of a positive opinion was 350 days. As noted above, three of these products have not been approved by FDA: Ceplene, Mepact, and Yondelis, aimed at acute myeloid leukemia, bone cancer, and advanced soft tissue sarcoma, respectively.[15–17] Approval

EXHIBIT 1

New Oncology Drugs Approved By The FDA Or The EMA, 2003–10

		Submission date		Days between submission date and approval date		
US trade name	**Active ingredient**	**FDA**	**EMA**	**FDA**	**EMA**	**Days between US and EC authorization to market**
Bexxar	Tositumomab	14-Sep-00	—	1,016	—	—
Velcade	Bortezomib	21-Jan-03	31-Jan-03	112	358	349
Erbitux	Cetuximab	14-Aug-03	1-Jul-03	182	267	138
Alimta	Pemetrexed disodium	30-Sep-03	29-Jul-03	127	330	229
Avastin	Bevacizumab	30-Sep-03	4-Dec-03	149	322	321
Vidaza	Azacitidine	29-Dec-03	9-Jan-08	142	288	1,673
Clolar	Clofarabine	30-Mar-04	27-Jul-04	273	579	517
Kepivance	Palifermin	15-Jun-04	2-Jul-04	183	390	314
Tarceva	Erlotinib hydrochloride	30-Jul-04	26-Aug-04	111	301	305
Revlimid	Lenalidomide	7-Apr-05	28-Feb-06	264	387	534
Arranon	Nelarabine	29-Apr-05	26-May-06	182	391	663
Nexavar	Sorafenib tosylate	8-Jul-05	7-Sep-05	165	232	211
Sutent	Sunitinib malate	11-Aug-05	30-Aug-05	168	240	174
Dacogen	Decitabine	15-Nov-05	—	168	—	—
Sprycel	Dasatinib	28-Dec-05	12-Jan-06	182	252	145
Vectibix	Panitumumab	29-Mar-06	28-Apr-06	182	510	432
Zolinza	Vorinostat	7-Apr-06	29-Oct-07	182	—	—
Tykerb	Lapatinib ditosylate	13-Sep-06	4-Oct-06	181	568	455
Tasigna	Nilotinib hydrochloride monohydrate	29-Sep-06	5-Oct-06	395	350	21
Torisel	Temsirolimus	5-Oct-06	5-Oct-06	237	350	173
Provenge	Sipuleucel-T	13-Nov-06	—	1,263	—	—
Ixempra kit	Ixabepilone	16-Apr-07	5-Oct-07	183	—	—
Treanda	Bendamustine hydrochloride	20-Sep-07	22-Nov-09	182	116	728
Firmagon	Degarelix acetate	28-Feb-08	27-Feb-08	300	295	55
Mozobil	Plerixafor	16-Jun-08	5-Jun-08	182	358	228
Afinitor	Everolimus	30-Jun-08	1-Jul-08	273	332	126
Votrient	Pazopanib hydrochloride	19-Dec-08	27-Feb-09	304	356	238
Istodax	Romidepsin	12-Jan-09	—	297	—	—
Arzerra	Ofatumumab	30-Jan-09	5-Feb-09	269	349	175
Folotyn	Pralatrexate	24-Mar-09	—	184	—	—
Halaven	Eribulin mesylate	30-Mar-10	—	230	—	—
Jevtana kit	Cabazitaxel	31-Mar-10	—	78	—	—
Ceplene	Histamine dihydrochloride	—	6-Oct-06	—	656	—
Mepact	Mifamurtide sodium	—	3-Nov-06	—	776	—
Yondelis	Trabectedin	—	27-Jul-06	—	357	—

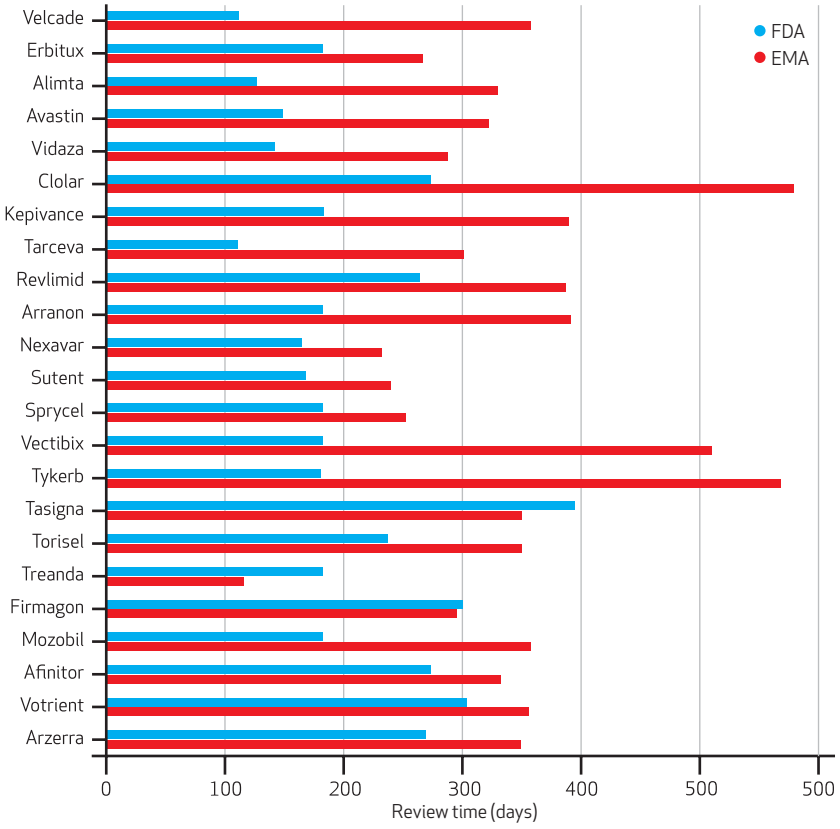
SOURCE Authors' analysis of data from online Food and Drug Administration (FDA, http://www.fda.gov) and European Medicines Agency (EMA, http://www.ema.europa.eu) databases. **NOTES** Drugs are listed in chronological order according to when they were submitted to the FDA. The three that have not been approved by the FDA are listed at the end, because their FDA submission dates are not publicly available. EC is European Commission.

of Ceplene in the European Union was granted only after a secondary review cycle under exceptional circumstances.[18] For both Mepact and Yondelis, the FDA decided against approval after advisory committees voted that these drugs had not demonstrated benefits that would outweigh their probable risks.

Exhibit 2 shows the review times for the twenty-three new oncology drugs that have been approved by both agencies since 2003. Of these, the EMA had a faster review process for only three: Treanda, Tasigna, and Firmagon, which target chronic lymphocytic leukemia, chronic myelogenous leukemia, and prostate cancer, respectively.[19–21] In the case of Treanda, however, the product was approved in the United States before it was submitted to the EMA. Furthermore, because of the delay between positive EMA opinions and the European Commission's adoptions of those opinion, Tasigna and Firmagon were still on the market in the United States before they were in Europe. Therefore, all twenty-three of the products approved by both agencies were available to US patients before

EXHIBIT 2

Review Times Of New Oncology Drugs Approved By The FDA And The EMA, 2003–10



SOURCE Authors' analysis of data from online Food and Drug Administration (FDA, http://www.fda.gov) and European Medicines Agency (EMA, http://www.ema.europa.eu) databases.

European patients.

Using an unpaired *t*-test, we determined that this delay in time to market was statistically significant. The median delay was 238 days, and the mean delay was 138 days (95% confidence interval: 89, 187) in favor of the FDA.

Discussion

Cancer is arguably the most feared disease, or set of diseases, facing humanity. The symptoms of cancer can be severe and debilitating, and a cancer diagnosis is often perceived as a death sentence. Although there are some risk factors that predispose people for particular cancers, cancer can strike anyone at any time. Given that the lifetime risk of developing cancer is 30–50 percent, even those without cancer probably have close friends or relatives who have battled or succumbed to the disease.

Many cancers can be cured surgically, and some can be cured with radiation and chemotherapy. However, there is no curative therapy for most metastatic cancers—that is, a cancer that starts in one part of the body and spreads to another—and often not even a therapy that extends the patient's life. This unmet medical need has made cancer a focus of the public's evaluation of the process and regulation of drug development. The media frequently use images of dying cancer patients desperately waiting for FDA-approved therapies to invoke public ire at the time-consuming nature of this process, and particularly how long the FDA review takes.

Contrary to repeated public assertions, we found that new oncology medicines are consistently available in the United States before they are in Europe, and they are more likely to be approved by the FDA than by the EMA. Moreover, the median time for approval in the United States was just six months.

INITIAL AND SUPPLEMENTARY APPROVALS Our analysis was specifically limited to initial approvals of drugs. However, supplemental approvals for secondary uses constitute a sizable proportion of oncology drug approvals and are a major route of advancing cancer care.

Although an analysis of supplementary approvals of oncology medicines in Europe and the United States could reveal a trend that differs from what we found with initial approvals, the availability of new anticancer drugs—and hence, initial approvals—are of primary concern. After all, once drugs gain initial approval, they can also be used for off-label indications, as is commonly the case in oncology. The practice of off-label drug use can include using a drug to treat a clinical condition or patient population other than the one for which the drug was approved. The National Comprehensive Cancer Network, an alliance of twenty-one leading cancer centers in the United States, estimated in 2004 that 50–75 percent of all prescriptions for cancer therapies were off-label.[22]

Because it is not feasible to test every new drug against multiple cancers, particularly rare tumors, Medicare is required to cover off-label cancer therapies that are recommended in approved drug compendiums.[23] Therefore, although the rate at which critical new uses are added to labeling is important and will be a focus of future study, the initial approval of new drugs and biologics in the field of oncology serves as a critical market entry point.

EXPEDITED REVIEWS The FDA is often accused of being slow to approve oncology drugs. However, critics have not provided specifics, and our study plainly shows that such assertions are unwarranted. The rapid approval of oncology drugs is not accidental, nor is it surprising. The FDA has long sought to conduct more rapid reviews of drugs with greater therapeutic potential, particularly anticancer drugs.[24]

Oncology drug development is distinctive in

The rapid approval of oncology drugs is not accidental, nor is it surprising.

that anticancer drugs and biologics are much more likely than drugs in other therapeutic areas to be given priority review ratings or to take advantage of accelerated review mechanisms. For example, Joseph DiMasi and Henry Grabowski found that in the period 1990–2005, 71 percent of oncology drugs received a priority review designation, and 47 percent received accelerated approval, compared to 40 percent and 13 percent, respectively, for all other drug classes.[26] A priority review designation is intended for drugs that are expected to offer major advances in treatment or to provide a treatment for a condition that has no adequate therapy. This designation reduces the expected FDA review time for a drug: The goal for completing a priority review is only six months, as opposed to the ten-month goal for a standard review. Accelerated approval allows the FDA to approve a drug based not on clinical benefits but on surrogate endpoints considered likely to predict those benefits—for example, tumor shrinkage may be considered likely to predict longer survival.

The hope is that these advantages will offset the inherent difficulties of conducting clinical trials in oncology. One challenge is the slow acquisition of patients for trials, a phenomenon with many contributing factors—such as patients' or physicians' lack of information about trials, patients' fear of receiving placebo or a poor treatment, the rarity of some cancers, and confounding factors that may make a patient ineligible for a trial.[25]

A second challenge is the particularly long times needed to establish a drug's efficacy, in part because of the slow acquisition of patients and also the need to measure survival over a period of years. In making these advantages available, the FDA recognizes the serious unmet medical need that continues to exist in the field of cancer.[26,27] Similar expedited review mechanisms exist in Europe and are frequently used there to designate oncology medicines as a priority.

SPEED VERSUS SAFETY In contrast to those who criticize the FDA for slow drug reviews, others believe that the agency approves applications too quickly, sacrificing safety for speed and quality for quantity.[28] Indeed, the balance between speeding treatments to critically ill patients and ensuring that those treatments are safe is a delicate one.

Increased review speed has been associated in some studies with increases in serious adverse drug reactions.[29] Other studies have determined that this association disappears when one controls for factors such as the novelty of the mechanism of a new drug and drugs approved with anticipated risks that are expressed in the form of so-called black-box warnings—a warning in the labeling, in which the FDA describes a known serious risk.[30] Although such factors are often applicable to anticancer drugs and biologics, the vast majority of anticancer drugs have good track records for safety.[31]

However, agencies such as the FDA and the EMA recognize the efficiency to be gained by harmonizing drug development around the world. Also, national governments appreciate the need for additional investment in postmarketing safety surveillance and health information technology. As a result of these initiatives to improve both safety and efficiency, drug lags between Europe and the United States will probably decrease.

THE PRESCRIPTION DRUG USER FEE ACT Over the past two decades, the pace at which the FDA reviews drugs has improved considerably, and review times have been shortened.[32] The changes are in large part due to the Prescription Drug User Fee Act of 1992. The law was intended to address a major backlog in new drug applications at the FDA. It gave the agency authority to collect fees from companies that produce certain drugs and biological products, both when the companies submit an application to have a new product approved, and for each drug that they have on the market. This money is added to the budget that Congress appropriates for the FDA; in exchange, the FDA accepts overall performance goals, which emphasize review timeliness as well as other measures. This set of policy initiatives, as well as the establishment of programs such as accelerated approval, has helped alleviate concerns that potentially life-saving therapies were encountering unnecessary delays in the review process, which prevented patients from taking advantage of them.

Subsequent reauthorizations of the Prescription Drug User Fee Act, which occur every five years, have given the FDA new authorities and increased the user fees to meet other needs of the agency. But it is widely agreed by experts in drug regulatory matters—including staff members of the FDA—that the science of developing new tools, standards, and approaches to assess the

safety, efficacy, quality, and performance of FDA-regulated products must advance considerably. For example, as the FDA itself has noted, the vast trove of data stored at the FDA must be transformed into a harmonized format and organized in a common database so that it can be queried by topic and analyzed to address key questions. This, in turn, will require investments in informatics hardware and software and the development of standardized data models for relational databases and scientific computing. With such a common platform in place, scientists could take advantage of existing historical data as well as new data to make better decisions in the context of regulatory review and oversight.

However, user fees are not sufficient to support such regulatory scientific advancement, nor are they an appropriate source of funds for that purpose. Instead, strong public support and additional congressional appropriations are required to move the FDA forward.

As the next reauthorization of the Prescription Drug User Fee Act, scheduled for 2012, draws closer, it is important to examine critically the successes and failures of the current regulatory process. Areas needing improvement must be identified, and appropriate measures devised. Given our findings—that the FDA has approved more new oncology drugs than the EMA has, and that it has approved these drugs more quickly—increasing the speed of drug review times might not be as high a priority as achieving other objectives in advancing regulatory science.

Conclusion

Although our results are applicable only to oncology medicines, they are consistent with FDA Commissioner Margaret Hamburg's comment in a letter to the editor of the *Washington Post* that the FDA's review times of all new drugs are typically shorter than those of the EMA.[33] Our results are also consistent with other studies that indicate that the lack of new oncology medicines is due not to slow review processes, but rather to difficulties in carrying out clinical trials in the field of oncology.

Science at all levels must continue to advance for the good of patients.

Innovative trial designs and development pathways are needed to translate advances in basic science into effective therapeutic options. One example would be permitting adaptive clinical trials—which would allow modifications to be made to an ongoing clinical trial, such as redirecting patients to different trial arms based on accumulating results and therefore increasing the chance of response.

Another example would be creating a regulatory pathway that would allow for simultaneous development of drugs and diagnostics. Such a combined pathway could allow for simultaneous regulatory approval of a diagnostic test to ascertain that a patient had a particular type of cancer with a specific genetic profile, and of a new drug expressly targeted for that type of cancer. These types of drugs and diagnostics already exist, and there could be hundreds if not thousands more of them in the future.

Contrary to the assertions of many critics, then, this article makes clear that the FDA should be congratulated for its swift review of new oncology medicines. However, science at all levels—basic science in the lab and regulatory science at the FDA—must continue to advance for the good of patients. As a result, continued financial support, in the form of user fees and increased appropriations, will be crucial for the agency to keep pace with current scientific discovery—and to maintain and enhance the agency's critical role of bringing new medicines from the stages of discovery into the clinic and ultimately improving the lives of patients. ■

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