# A Drug's Life: The Pathway to Drug Approval

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**Abstract**: In the United States, drugs and medical devices are regulated by the US Food and Drug Administration (FDA). A drug must undergo rigorous testing prior to marketing to and medical use by the general public. The FDA grants marketing approval for drug products based on a comprehensive review of safety and efficacy data. This review article explains the history behind the establishment of the FDA and examines the historical legislation and approval processes for drugs, specifically in the fields of medical oncology and hematology. The agents imatinib (Gleevec, Novartis) and decitabine (Dacogen, Eisai) are used to illustrate both the current FDA regulatory process—specifically the orphan drug designation and accelerated approval process—and why decitabine failed to gain an indication for acute myeloid leukemia. The purpose and construct of the Oncologic Drugs Advisory Committee are also discussed, along with examples of 2 renal cell cancer drugs—axitinib (Inlyta, Pfizer) and tivozanib—that used progression-free survival as an endpoint. Regulatory approval of oncology drugs is the cornerstone of the development of new treatment agents and modalities, which lead to improvements in the standard of cancer care. The future landscape of drug development and regulatory approval will be influenced by the new breakthrough therapy designation, and choice of drug will be guided by genomic insights.

## Introduction

Imagine it is 1890, and you have spent months suffering from terrible jaw pain caused by cancer. You see a traveling performance troupe advertising Hamlin's Wizard Oil, a purported cure for rheumatism, cancer, pneumonia, hydrophobia, and many other ailments.[1] Its slogan states, "There is no sore it will not heal, no pain it will not subdue," which sounds perfect for your situation.[2] Desperate for relief, you purchase a bottle of the preparation for $0.35 and start taking it.

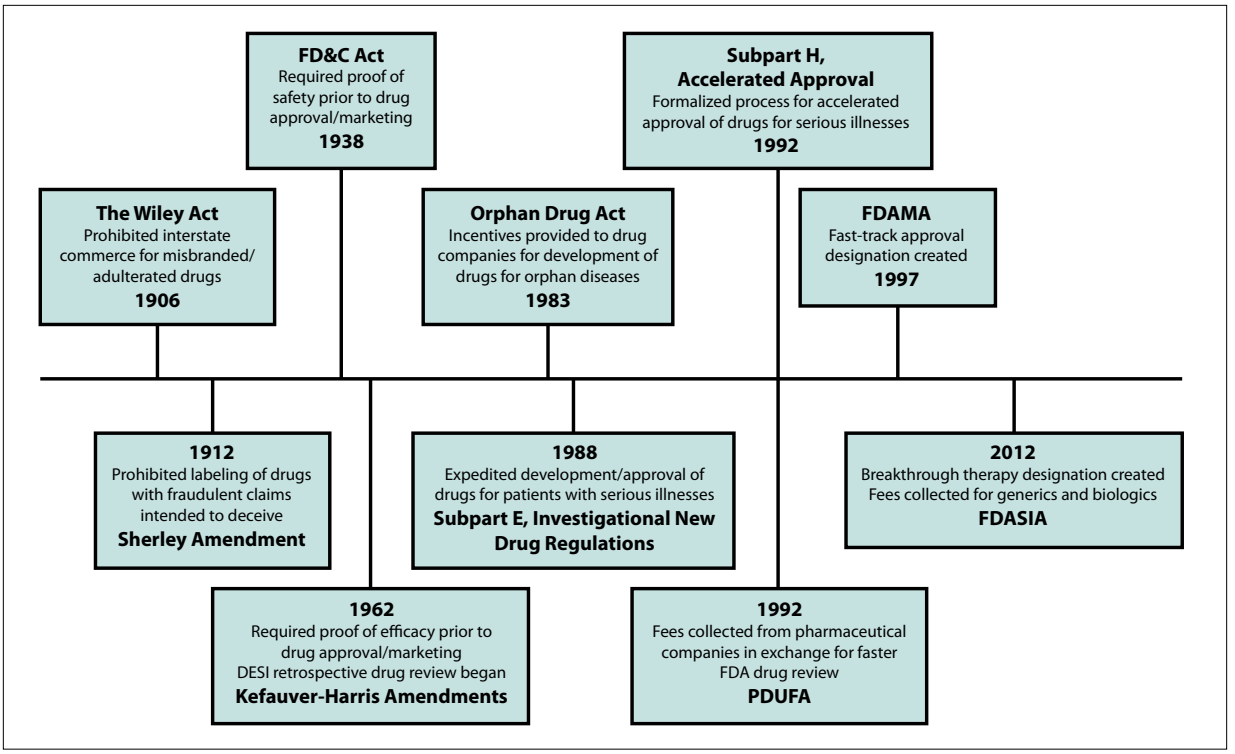


**Figure 1.** Timeline of key legislation for the US Food and Drug Administration.

DESI, Drug Efficacy Study Implementation; FD&C Act, Federal Food, Drug, and Cosmetic Act; FDAMA, Food and Drug Administration Modernization Act; FDASIA, Food and Drug Administration Safety and Innovation Act; PDUFA, Prescription Drug User Fee Act.

Months later, you are weaker than before, have developed a gastric ulcer, and are in pursuit of another treatment. A doctor tells you that the cancer has progressed too far to treat, and that only palliative options are available.

The US Food and Drug Administration (FDA) was established in large part to put an end to nostrums and other medicinal quackery, and establish a pathway for drug approval. What has resulted is a highly sophisticated process of drug development and approval that provides citizens with safe treatments that are proven to be effective. Figure 1 displays the historical legislation of the FDA.

## The End of an Era

Prior to 1906, people in the United States had complete freedom to create and market any food or drug in any way and for any purpose.[3,4] Numerous preparations, such as Hamlin's Wizard Oil, were marketed during this era as treatments for a variety of ailments without any proof that they worked. Many of these treatments did not even contain what was claimed to be in the preparation. Progress toward regulation of food and drugs began around 1902 when Dr Harvey Washington Wiley, chief chemist of the Bureau of Chemistry of the US Department of Agriculture, started assessing drug ingredients and found many of them to be misbranded and/or adulterated.[3,4] This eventually led to the Pure Food and Drugs Act of 1906 (The Wiley Act), which prohibited falsely labeled or contaminated food and drugs in interstate commerce.[3-5] A 1912 amendment to the Wiley Act, called the Sherley Amendment, prohibited manufacturers from labeling medications with erroneous therapeutic claims intended to defraud the customer. Although this was a step in the right direction, it was difficult for the FDA to prove intent.[3]

## Tragedy Strikes, Rules Change

Many changes in US drug regulation have been in response to tragedies both in the United States and around the world. In 1937, more than 100 people in the United States, including many children, died owing to ingestion of a product called Elixir Sulfanilamide. This liquid preparation of sulfanilamide contained diethylene glycol as the base solution, and was never examined for safety. At that time, legislation requiring verification of safety prior to bringing a drug to the market did not exist. This meant that the FDA was only able to charge the manufacturer with misbranding, as the drug was labeled as an elixir when it did not contain alcohol.[3] The Federal Food, Drug, and Cosmetic Act (FD&C Act)

was consequently passed in 1938. This act completely overhauled the public health system, and authorized the FDA to demand proof of safety prior to drug approval.[3,6]

The Kefauver-Harris Amendments, which were passed in 1962, made proof of efficacy a requirement for drug approval for the first time. Manufacturers were required to prove drug efficacy of both prescription and over-the-counter drugs by providing adequate and well-designed studies.[3] As with the FD&C Act, the legislation occurred in response to a tragedy—this time from the use of the drug thalidomide (Thalomid, Celgene).[3,6] Thalidomide first gained approval in Germany in 1958 as an anticonvulsant. By 1961, it was widely prescribed to pregnant women in more than 48 countries for morning sickness. It was only after widespread use of thalidomide that it was recognized to cause horrible birth defects, including phocomelia. More than 8000 infants were affected in Europe.[7]

In the United States, FDA approval of thalidomide was delayed owing to concerns of the chief of the Division of New Drugs regarding the incidence of peripheral neuropathy.[3,7] Although more than 2.5 million tablets were given to 1267 physicians and distributed to more than 20,000 patients in clinical trials in the United States, only 17 infants were affected. (Thalidomide was reintroduced into the US market in 1998 as a treatment for leprosy, in conjunction with stringent prescribing restrictions.[7])

For those drugs already on the market, the Kefauver-Harris Amendments originated the Drug Efficacy Study Implementation (DESI) review process. Drugs approved by the FDA between 1938 and 1962 (designated DESI drugs) were required to undergo retrospective review for safety and efficacy. The downside of this process was the creation of a large backlog of unreviewed drugs; many drugs became available in foreign markets before they became available in the United States.[3,8]

## Drugs for all Diseases, and Quickly!

In an attempt to increase the development of drugs for "orphan" diseases—those that impact a small number of patients in the United States—the Orphan Drug Act was passed in 1983. This act provides incentives to pharmaceutical companies for the development of drugs for unusual conditions that do not have adequate treatments and for which the pharmaceutical company is anticipated to incur a financial loss.[4,9] This act has dramatically increased the availability of drugs that would not be developed otherwise.[10]

Another tragedy that had a significant impact on FDA regulations was the onset of the AIDS crisis in the late 1980s. This crisis led to subpart E of the Investigational New Drug Application (IND) regulations in 1988. Subpart E permitted a hastened FDA approval process for new drugs to treat serious and life-threatening illnesses and conditions, and made experimental drugs intended for those diseases more widely available. The regulations highlighted the importance of close communication between the FDA and the drug sponsor throughout the FDA approval process, including meetings conducted prior to IND submission and at the end of phase 1 studies. The goal is to improve the efficiency of preclinical and clinical study development and to assist with agreement between the FDA and drug sponsor on the clinical studies needed to ensure FDA approval.[4,11]

The next major change in FDA regulations came in 1992, with subpart H (accelerated approval) to NDAs, which has become particularly germane to cancer drugs. Accelerated approval expedited the approval process for drugs used to treat serious or life-threatening illnesses and conditions, and included the potential for FDA approval based upon a surrogate endpoint of a drug's effectiveness.[4,11,12]

Despite these advances in the drug approval process, pharmaceutical companies remained concerned with its efficiency and predictability. As a result, pharmaceutical companies began to provide funding to help expedite the process through the Prescription Drug User Fee Act (PDUFA) and the Prescription Drug Amendments of 1992. These pieces of legislation authorized the FDA to collect fees from drug companies that produced specific human drug and biological products in order to bolster the FDA's resources. In return, the FDA agreed to set time goals for the review of New Drug Applications (NDAs). Goals for improving communication and the timeline of meetings between the FDA and drug sponsor were determined. The PDUFA must be reauthorized every 5 years, and is now in its fifth revision.[4,13,14]

## Continual Improvement

The Food and Drug Administration Modernization Act (FDAMA) of 1997 was passed to reform the regulation of drugs, food, devices, and biological products. This act changed the approval process for biological agents so that the process matched that of drug approval, and created the fast-track approval process designation. Fast-track designation expedites the approval of drugs that fill an unmet medical need for serious diseases.[3,15] Drug approval for the pediatric population was improved through the passage of the Best Pharmaceuticals for Children Act (BPCA) in 2002, which was designed to improve the safety and efficacy of pharmaceuticals for children.[16] Under the FDA Amendments Act of 2007, the BPCA was reauthorized and the Pediatric Equity Act (PREA), designed to encourage more research into the development of treatments for children, was enacted.[17]

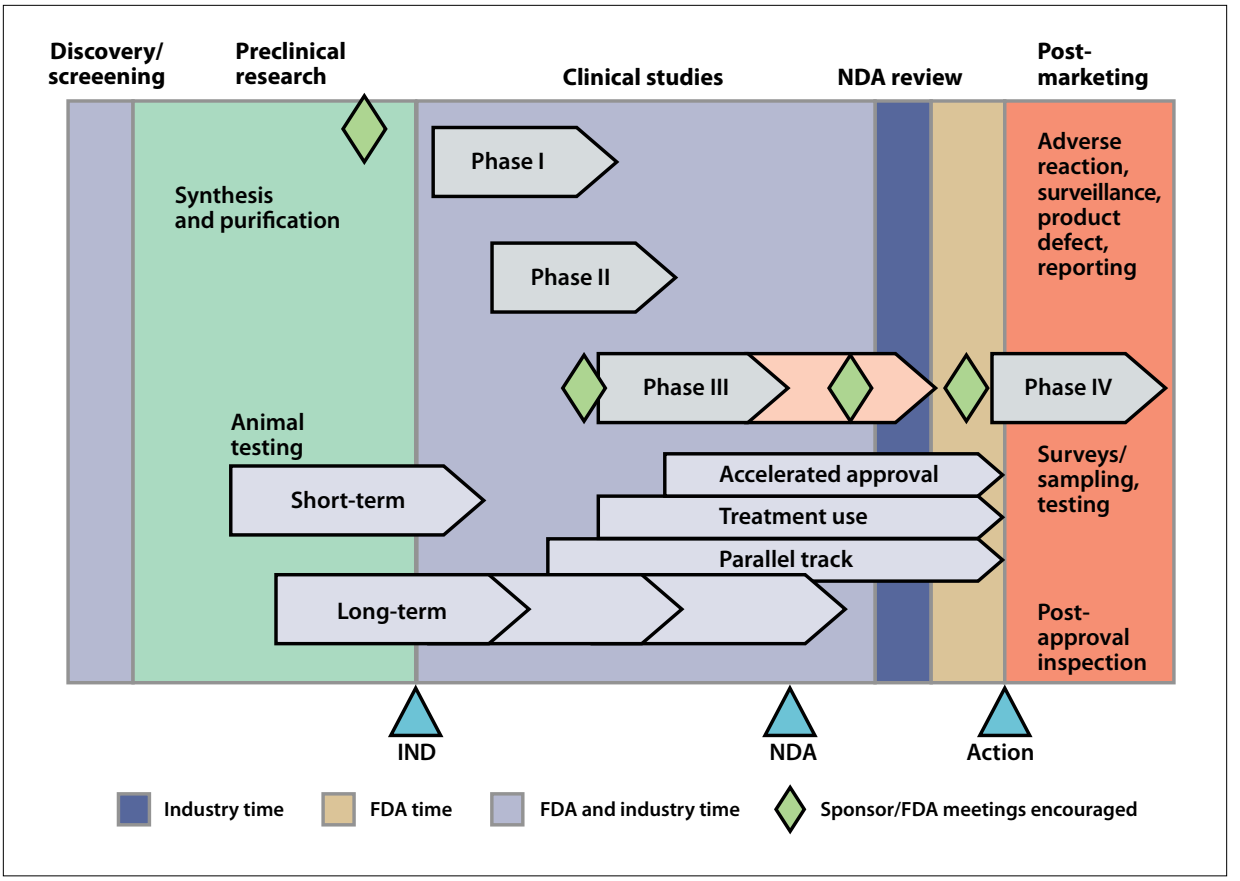


**Figure 2.** The US Food and Drug Administration drug approval process involves a number of steps, including preclinical and clinical studies, and, later, postmarketing research.

FDA, Food and Drug Administration; IND, Investigational New Drug Application; NDA, New Drug Application.

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More recently, the Food and Drug Administration Safety and Innovation Act (FDASIA) was passed in 2012. This reauthorized the PDUFA through 2017 and permitted the FDA to collect funds for other products.[18] The Generic Drug User Fee Amendments of 2012 allowed the FDA to receive funds from the generic drug industry, while the Biosimilar User Fee Act of 2012 enabled the FDA to receive funds from the biopharmaceutical drug industry in return for a shortened time to review by the FDA; the goal is for 90% of applications to be acted upon within 10 months of submission.[19,20] Drug approval for the pediatric population was encouraged through the reauthorization of the BPCA and PREA and the creation of the Pediatric Medical Device Safety and Improvement Act.[21] Notably, the breakthrough therapy designation was formed to further shorten the time for approval of new drugs that treat serious or life-threatening conditions.[22,23] Drugs that gain this designation earn the same benefits as those with fast-track designation, in addition to receiving more intensive FDA guidance on implementing an efficient drug development program.[22,23]

## The Current Standard Drug Approval Process

The drug approval process typically takes approximately 8 to 10 years from the initial discovery of a drug to receipt of FDA approval, and follows certain standard steps (Figure 2).[24-26]

All drugs start with preclinical testing, including tests in in vitro models and in animals. Information on the drug's toxicity and an efficacy profile are used in determining the lethal dose of the drug and the safe initial dose for human studies.[24] Although most of these drugs never make it to human testing or to review by the FDA, these results form the basis of an IND. The FDA reviews the IND to ensure that the planned human studies do not place patients at an undue risk of harm, and that there is adequate informed consent and human subject protection. Phase 1 studies are then conducted to ascertain the safety profile of the drug and to determine the maximum tolerated dose, along with information about pharmacokinetics and pharmacodynamics. These are fol-

lowed by phase 2 studies in a larger group of patients who have the disease or condition of interest, with a goal of determining the drug's efficacy while continuing to assess safety. Phase 3 studies follow; these are randomized trials that compare a new drug or drug combination with placebo or standard of care treatment. The primary endpoint is always some measurement of efficacy, along with continued collection of safety data.[24,25,27]

Meetings between the FDA and the drug sponsor may occur at multiple times following the submission of the IND, but the FDA strongly encourages a meeting following the completion of phase 2 studies and prior to the start of phase 3 studies. At this time, the FDA and the drug sponsor try to agree on how the phase 3 studies should be conducted. Upon the completion of phase 3 studies (or rarely, following phase 2 studies), the drug sponsor will submit an NDA to seek formal FDA approval.[24,25,27] The NDA includes all animal and human data with interpretation, pharmacokinetic and pharmacodynamic data, and manufacturing details. Sometimes, the FDA will call upon advisory committees, such as the Oncologic Drugs Advisory Committee (ODAC), for expert opinion and recommendations regarding the drug application. If the drug is approved, the FDA will designate postmarketing requirements and commitment studies (phase 4 studies) to be conducted by the sponsor to gather additional information about the drug's efficacy, safety, and optimal use.[24,26]

## Accelerated Approval Pathways

### *Priority Review*

There are 2 review tracks for NDAs: traditional and priority. Traditional review designation is given to drugs that offer some improvement over existing therapy. Priority review designation is given to drugs that offer a significant advancement in therapy or that target an indication for which no adequate therapy exists. The priority designation provides the drug sponsor with additional FDA resources and attention for quicker review of the NDA. After a drug sponsor requests priority review, the FDA has 45 days to respond.[28]

### *Accelerated Approval*

Accelerated approval may be granted to new drugs used in serious or life-threatening illnesses that do not have acceptable treatments. For those drugs, approval may be granted based upon a surrogate endpoint likely to translate to a clinically meaningful outcome. Approval of the drug is accompanied by an agreement between the FDA and the drug sponsor to complete postmarketing studies to confirm the anticipated clinical benefit. If this occurs, the drug will be granted traditional approval. Conversely, if studies do not confirm the clinical benefit, the FDA may remove the drug or drug indication from the market.[12,27,28]

### *Fast-Track Designation*

To gain fast-track designation, a drug must be used to treat a serious or life-threatening condition and fill an unmet medical need. Drugs that achieve fast-track designation are eligible for additional meetings with the FDA to discuss the development plan. Accelerated approval may also be granted. Most drugs eligible for fast-track designation are also eligible for priority review, which speeds up the review and approval process. An application for fast-track designation can be submitted at any time during the drug development process. The FDA must provide a response to the sponsor within 60 days.[28]

### *Breakthrough Therapy Designation*

To gain breakthrough therapy designation, which is the newest designation in the FDA drug approval process, initial clinical data for a new drug must show substantial improvement over available therapy on at least 1 clinically significant endpoint. This is in contrast to fast-track designation, in which the drug must demonstrate clinical or nonclinical potential to address an unmet medical need. This designation includes even more intense FDA guidance on an efficient drug development program. A cross-disciplinary project lead for the FDA review team is designated to aid in the review program and to be a scientific liaison for the cross-discipline review team (clinical, pharmacology-toxicology, chemistry, manufacturing, compliance, and control). Application for this designation can be done at any time during the drug development process. The FDA must provide a response to the sponsor within 60 days.[22,23]

## The Drug Approval Battlefield: A Win and a Loss

### *Imatinib*

The history of imatinib (Gleevec, Novartis) exemplifies the efficiency of the FDA's current drug approval process. Imatinib was developed as a specific inhibitor of the BCR-ABL tyrosine kinase for patients with Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML).[29-32] The regulatory highlights of imatinib development are listed in Table 1. The time from the first patient enrollment onto the initial phase 1 clinical trial to submission of a NDA was 32 months. This was almost half the usual time for a new drug, as it was placed on the accelerated approval pathway with an orphan drug indication. Moreover, the NDA for imatinib was then approved in 2½ months, which is the shortest time to approval for any cancer drug.[33-35]

**Table 1.** Important Milestones in Imatinib Mesylate's Approval History

| Date | Regulatory Action |
|---|---|
| April 9, 1998 | Initial phase 1 clinical trial submitted |
| June 22, 1998 | First patient enrolled in phase 1 clinical trial |
| July 14, 1999 | Fast-track designation for CML blast crisis |
| July 15, 1999 | BC- and AP-CML protocols submitted |
| July 26, 1999 | First BC-CML patient enrolled |
| August 9, 1999 | First AP-CML patient enrolled |
| December 8, 1999 | INF-α failure, CP-CML protocol submitted and patient enrolled |
| January 31, 2001 | Orphan drug designation received |
| February 27, 2001 | Imatinib NDA submitted |
| May 10, 2001 | FDA granted accelerated approval for BC-CML, AP-CML, and CP-CML after INF-α failure |
| December 20, 2002 | FDA granted accelerated approval for newly diagnosed Ph+ CML in CP |
| December 8, 2003 | FDA converted accelerated approval to full approval for BC CML, AP CML, and CP CML after INF-α failure |
| September 29, 2006 | FDA converted accelerated approval to full approval for newly diagnosed Ph+ CML |

AP, accelerated phase; BC, blast crisis; CML, chronic myeloid leukemia; CP, chronic phase; FDA, Food and Drug Administration; INF-α, interferon-α; NDA, New Drug Application; Ph+, Philadelphia chromosome–positive.

In 2001, imatinib was granted accelerated approval for the treatment of CML in blast crisis (BC), accelerated phase (AP), or chronic phase (CP) after progression on interferon-α (IFN-α) treatment. Accelerated approval was granted on the basis of results from 3 single-arm studies conducted in patients with Ph+ CML.[31,36-39] A total of 1027 patients were enrolled in these studies, which evaluated cytogenetic response rate (in patients with CP-CML) and hematologic response rate (in patients with AP- and BC-CML) as primary endpoints. The cytogenetic response rate for patients with CP CML was 49%, and the hematologic response rates for patients with AP and BC CML were 63% and 29%, respectively. Cytogenetic and hematologic response rates were used as surrogate endpoints for overall survival (OS) and progression-free survival (PFS) because the length of follow-up and study size needed to determine OS differences would be excessive, particularly for CP CML.

After accelerated approval was granted, the sponsor was required to provide long-term safety and efficacy follow-up of the 3 single-arm studies, in addition to completing a randomized phase 3 study comparing imatinib with a combination of IFN-α and cytarabine in patients with newly diagnosed CP CML.[31,39] This came in the form of 532 patients with CP CML with a median follow-up duration of 29 months. A complete hematologic response was achieved in 95% of patients, and 87.8% of patients who achieved a major cytogenetic response maintained the response for 2 years. After 2 years of treatment, OS was 90.8%. Hematologic response rates for patients with BC and AP CML were similar to those observed in the initial interim analyses, with a median duration of 10 months for patients in BC and 28.8 months for patients in AP.[35] In 2003, accelerated approval of imatinib for the treatment of CML in BC, AP, or CP after IFN-α therapy was converted to regular approval based on these follow-up data.[35,39]

Further clinical studies[39-41] allowed imatinib to be approved in 2006 for the first-line treatment of adults with Ph+ CML.

### *Decitabine*

Decitabine (Dacogen, Eisai) is a deoxynucleoside analogue of cytidine, a DNA methyltransferase inhibitor initially approved by the FDA for the treatment of myelodysplastic syndromes (MDS) in 2006.[42] Decitabine's sponsor, Eisai, worked with the FDA in an attempt to expand its indication to include acute myeloid leukemia (AML), as options are limited for AML patients who may not be able to tolerate intensive induction chemotherapy.[43]

In May 2006, the FDA and the European Medicines Agency (EMA) granted orphan designation to decitabine for the treatment of AML. By May 2011, Eisai submitted a supplemental NDA to expand decitabine's indication to include the treatment of AML in adults 65 years of age and older who are not considered candidates for intensive chemotherapy.[42] The regulatory highlights of decitabine development are listed in Table 2.

Decitabine was evaluated for its utility in AML patients in the phase 2 DACO-017 and phase 3 DACO-016 (Study of Decitabine for Treatment of Older Patients With Acute Myeloid Leukemia) studies.[44,45] The supportive-open label DACO-017 trial evaluated the efficacy of decitabine as first-line therapy in older AML patients, who received decitabine for a median of 3 cycles. The primary endpoint was morphologic complete remission (CR), and OS was a secondary endpoint. Morphologic CR was assessed by an external expert reviewer and was achieved in 23.6% of patients; median OS was 231 days.[44]

In contrast to DACO-017, DACO-016 was a randomized, controlled, open-label, multicenter study that

**Table 2.** Important Milestones of Decitabine's Approval History for Indication of Acute Myeloid Leukemia

| Date | Regulatory Action |
|---|---|
| May 2, 2006 | FDA approval for MDS |
| March 12, 2010 | FDA approval for outpatient regimen of MDS |
| February-August 2005 | Communication between sponsor and FDA regarding SPA for DACO-016 |
| March 2005 | Patient enrollment for DACO-017 |
| January 2006 | Patient enrollment for DACO-016 |
| May 2006 | Orphan drug designation received for AML |
| February 1, 2008 | Cutoff date for data collection for DACO-017 |
| October 28, 2009 | Initial prespecified primary efficacy endpoint cutoff date for DACO-016 |
| February 22, 2010 | pre-sNDA teleconference between sponsor and FDA; agreement made for content and format of proposed AML sNDA |
| October 29, 2010 | New cutoff date by sponsor for a single, unplanned updated analysis for DACO-016 |
| May 6, 2011 | sNDA accepted for AML |
| February 9, 2012 | FDA's ODAC voted against approval for AML |
| March 6, 2012 | FDA did not approve for AML |
| July 19, 2012 | EMA approved for AML |

AML, acute myeloid leukemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; MDS, myelodysplastic syndromes; ODAC, Oncologic Drugs Advisory Committee; sNDA, Supplemental New Drug Application; SPA, Special Protocol Assessment.

compared decitabine with control treatment (low-dose cytarabine [LDAC] plus supportive care or supportive care alone) as first-line therapy for de novo or secondary AML patients with intermediate- or poor-risk cytogenetics. The DACO-016 study was conducted under a Special Protocol Assessment,[42] an agreement between the FDA and the sponsor on the design and size of a clinical trial that can be used for regulatory purposes. The prespecified primary endpoint of DACO-016 was OS, using an original data cutoff of October 28, 2009; this was the only endpoint that controlled for type 1 error. There was no statistically significant difference between decitabine and control treatment in median OS (7.7 months vs 5.0 months; *P*=.108) or mortality (hazard ratio [HR], 0.85; 95% CI, 0.69-1.04) when using the preplanned endpoint for analysis,[42,45-47] although an unplanned analysis incorporating 1 additional year of follow-up had a statistically significant better OS for decitabine.

Based on these data, the FDA's ODAC voted 10:3 (with 1 person abstaining) on February 9, 2012, that the data from the DACO-016 study did not support a favorable benefit to risk profile of decitabine for the treatment of AML.[46,48] ODAC members raised several concerns, including: response rate in the LDAC control arm in DACO-016 was lower than prior trials; patient-reported outcomes were not improved with decitabine compared with LDAC; and most importantly, the primary endpoint of OS was not met in the primary analysis. The FDA rejected approval of decitabine for the treatment of AML. Of note, while the EMA adopted a positive decision regarding decitabine in older AML patients, it has not approved decitabine for the treatment of MDS.

## Issues Discussed by the ODAC

The purpose of the ODAC is to review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer, and to make appropriate recommendations to the Commissioner of Food and Drugs. The committee consists of a core of 13 voting members, including 1 patient representative and 1 consumer representative, and 1 nonvoting industry representative.[49]

ODAC meetings occur when decisions about the relative balance of risks and benefits surrounding a cancer drug are not straightforward, and the FDA is seeking advice from a panel of experts regarding the best path forward. Recent issues that have been discussed during these meetings include the following: Is PFS a valid endpoint? What is the role of accelerated approval? What future issues are likely to confront the FDA and ODAC?

### *Is PFS a Valid Endpoint?*

The answer to the question of whether PFS is a valid endpoint depends on the context, and whether a PFS advantage for patients treated with a drug is clinically meaningful. The tyrosine kinase inhibitor (TKI) tivozanib, which came before the ODAC, was backed by a phase 3 study in which 517 patients with metastatic or locally recurrent renal cell carcinoma were randomly allocated 1:1 to either tivozanib or sorafenib (Nexavar, Bayer and Onyx) as first-line therapy.[50] The primary endpoint was PFS, as determined by an independent review committee (IRC). OS was a secondary endpoint. While the analysis of PFS showed a statistically significant improvement in PFS with tivozanib (HR, 0.80; *P*=.04) and a median PFS of 11.9 months in the tivozanib arm and 9.1 months in the sorafenib arm, the final analysis of OS showed a trend toward a detrimental effect on OS with tivozanib (HR, 1.25; *P*=.11), including a median OS of 28.8 months in the tivozanib arm and 29.3 months in the sorafenib arm. Patients initially randomized to the sorafenib arm were allowed to cross over to the tivozanib arm upon

progression, but no such mechanism existed for patients randomized initially to the tivozanib arm, and this may have influenced the differential OS. Patient-reported outcomes, as measured by the Functional Assessment in Cancer Therapy general instrument, did not differ between arms. The ODAC voted 13:1 that tivozanib did not demonstrate a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial. In this case, an improvement in PFS was not enough to warrant approval; it would have been unprecedented to vote for approval of a drug with a worse OS and no improvement in patient-reported outcomes. Furthermore, the study design bordered on unethical in countries where second-line TKIs were not available.

The application for axitinib (Inlyta, Pfizer), a TKI for advanced renal cell carcinoma that came before the ODAC, stands in contrast with that for tivozanib. Once again, the application was supported by a randomized, controlled, open-label, multicenter phase 3 trial comparing axitinib with sorafenib as second-line systemic therapy in 723 patients with metastatic renal cell carcinoma.[51] Patients were randomized to receive either axitinib or sorafenib, with a primary efficacy endpoint of PFS as assessed by an IRC. More than half of the enrolled patients had received prior therapy with the TKI sunitinib (Sutent, Pfizer), and 35% had received cytokines. This analysis also showed a significant improvement in PFS for patients treated with axitinib, at a median of 6.7 months vs 4.7 months for those treated with sorafenib (HR, 0.67; $P<.0001$), but this time an OS nonsignificantly favored axitinib at a median of 20.1 months vs 19.2 months for sorafenib (1-sided $P=.374$). In addition, and in contrast to the tivozanib application, approximately one-third of patients received subsequent therapy off-study, and this was similar between arms. The ODAC voted unanimously, 13:0, that the benefit to risk evaluation was favorable for axitinib treatment in patients with advanced renal cell carcinoma after failure of a first-line systemic therapy. In this scenario, the PFS advantage—although similar to what was seen in the tivozanib study—was viewed as clinically meaningful because patients had already failed prior active agents (and thus were likely considered further along in their disease); PFS and OS trends were similar; and the study was well-designed, with similarly treated patients both before and after the study was conducted.

### *What Is the Role of Accelerated Approval?*

As defined earlier, accelerated approval regulation allows earlier approval of drugs to treat serious diseases if they fill an unmet medical need; approval may be based on a surrogate endpoint. Inherent in the concept of accelerated approval is balancing the need to give patients with serious and life-threatening diseases access to promising new therapies as soon as possible, while also protecting patients from products that are subsequently shown to not provide clinical benefit, and from which the risks outweigh the benefits.[12,27,28]

Approximately half of accelerated approvals for oncology drugs have been based on single-arm trials. In discussing this issue, the ODAC came to several conclusions. Committee members overwhelmingly agreed that randomized controlled trials should be the standard, but that single-arm trials could be used in the setting of rare diseases (this may become much more relevant in the era of molecularly-defined targets within disease subsets) in instances in which the agent in questions demonstrates a high level of activity or a pronounced treatment effect when balanced against treatment toxicities.

Regardless of whether the pivotal trial leading to accelerated approval is single-armed or randomized, a subsequent controlled trial confirming clinical benefit is required—and ideally 2 trials—though this may not be possible for rare diseases or pediatric indications. ODAC members also felt that a well-designed development plan was needed prior to the filing of the accelerated approval application. Most also preferred that the sponsor have studies already ongoing at the time of application. If the subsequent trial does not confirm clinical benefit, the FDA may withdraw the drug label.[52]

This occurred with the drug bevacizumab (Avastin, Genentech/Roche) for metastatic breast cancer. Bevacizumab received accelerated approval from the FDA for metastatic breast cancer in 2008 based on a study in which patients treated with the drug, in combination with paclitaxel, had a PFS advantage of 5.5 months (in this case, PFS was considered a surrogate endpoint for OS) compared with paclitaxel alone, but no OS advantage.[53] Unfortunately, in what were supposed to be confirmatory studies enrolling almost 2000 women, PFS was actually less than in the initial study, and no quality of life or survival advantage could be demonstrated in the bevacizumab-containing regimens.

### *What Future Issues Are Likely to Confront the FDA and ODAC?*

FDASIA was signed into law on July 9, 2012, giving rise to the breakthrough therapy designation.[22,23] This category is intended to expedite the development and review of drugs for serious or life-threatening conditions, and drugs receiving this designation can be eligible for the accelerated approval pathway. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates that the drug may have substantial improvement on at least 1 clinically significant endpoint over available therapy. Recent examples of drugs identified as breakthrough therapies include: daratumumab, for multiple myeloma; lambrolizumab, for melanoma; and

palbociclib, for breast cancer. It is anticipated that this designation will shorten times from initial strong signals of efficacy to approval. What is not yet clear, however, is what interim marker of clinical benefit will prove to be a strong enough signal in earlier phase studies to warrant faster approval, and what confirmatory studies would be needed to maintain the approved indication.

Key to the concept of both accelerated approval and the breakthrough therapy indication is defining a surrogate endpoint that is considered reasonably likely to predict clinical benefit. This has become particularly challenging in the genomic era of cancer therapeutics, in which diseases are increasingly being defined by molecular markers and less emphasis is being placed on the tissue or organ that is affected. The result is dwindling patient populations for these specific drug targets. In the coming years, it is inevitable that both the FDA and ODAC will be considering drugs applied to smaller studies in finely defined populations and necessitating well-validated and reliable assays for detecting those molecular targets. Disease control that has traditionally been defined by morphologic or radiographic markers will be monitored with increasingly sophisticated assays that will detect minimal residual disease; molecularly-defined cancers will become potential drug targets and surrogate trial endpoints. This is occurring in real time in acute lymphoblastic leukemia. How this new age of drug targets, drug development, and trial endpoints will be managed has yet to be determined.

## Conclusion

The landscape of drug regulation in the United States has evolved over the last century. Since the original Pure Food and Drugs Act signed into law by President Theodore Roosevelt in 1906 and the inception of the FDA shortly thereafter, the FDA has radically altered and standardized the drug approval process. This is a tremendous feat, especially in the field of medical oncology and hematology, where innovation and drug development continue. Central to this issue is the rate at which important new therapies reach the public, for without new tools for cancer treatment, there can be little expectation for success. The FDA has continued its cooperation with drug development and pledged an impressive commitment with the National Cancer Institute to fight the war against cancer, as evidenced by the enactment of the National Cancer Act of 1971. The basic principal is for sound and quality science to be rapidly and effectively translated into new treatments that are delivered to the public in the form of FDA-approved therapies. The future landscape of drug development and regulatory approval, in the era of breakthrough designation and targets for drug use guided by genomic insight, will be an interesting one indeed.

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