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Article

ARTICLE

Overview of Oncology and Hematology Drug Approvals at US Food and Drug Administration Between 2008 and 2016

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Abstract

Background: We previously conducted an overview of oncology products reviewed by the Office of Oncology Drug Products in the Center for Drug Evaluation and Research at the US Food and Drug Administration for marketing approval and the regulatory actions taken during July 2005 to December 2007. There is a need to understand if the changes in the laws, regulations, and the organization that occurred after 2007 had any impact on the regulatory drug approvals. We present a detailed overview of hematology and oncology products reviewed by Office of Oncology Drug Products and Office of Hematology and Oncology Drug Products.
Methods: We identified all oncology–hematology applications that were submitted to the US Food and Drug Administration from January 1, 2008 through December 31, 2016, and reviewed the approval actions taken.
Results: During the study period, the Office of Hematology and Oncology Products approved 239 applications that supported 260 new indications. Of the 239 applications approved, 141 were approved via priority review and 98 were approved via standard review. Fifty-three of these applications were granted accelerated approval, 29 were converted from accelerated approval to regular approval, and 157 received regular approval. Since its promulgation in 2013, breakthrough designation status has been granted to 25.7% of applications. A variety of endpoints were used to support these approvals.
Conclusion: During the study period, despite changes in the regulations and organization, the Office of Hematology and Oncology Products consistently utilized regulatory mechanisms that expedite the development and approval of promising oncology and hematology drug products resulting in the approval of 260 new indications.

We previously reviewed the oncology products approved by the FDA between July 2005 and December 2007 (1). Since 2007, however, a number of changes have taken place to accommodate a dramatic increase in applications in oncology. The Office of Oncology Drug Products (OODP), created in July 2005 to oversee new drug applications and biologic licensing applications for oncological and hematological products, contained three divisions to accommodate the review of oncology products: Division of Drug Oncology Products, Division of Biologic Oncology Products, and Division of Medical Imaging and Hematology Products. In 2011, OODP was reorganized and renamed the Office of Hematology and Oncology Products (OHOP) based on disease-specific therapeutic areas and organized into four different divisions: Division of Oncology Products 1, Division of Oncology Products 2, Division of Hematology Products, and Division of Hematology Oncology Toxicology. This reorganization was intended to standardize and expedite the process of reviewing applications in oncology and hematology drug products.

In addition to the reorganization of the office responsible for clinically reviewing these applications, new regulations have changed the way products are regulated and approved. In 2007, the Food and Drug Administration Amendments Act (FDAAA) (2) was enacted by Congress, thereby widening FDA's authority to assess various safety issues. FDAAA reauthorized the Best Pharmaceuticals for Children Act (BPCA) (3) and the Pediatric

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Research Equity Act (PREA) (4) and granted FDA the ability to require post-marketing requirements (ie, safety studies) to assess safety issues related to an approved product, which had previously been voluntary. FDAAA also gave FDA the new authority to require Risk Evaluation and Mitigation Strategies (REMS) for approved products.

Finally, the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) (5) in 2012 added flexibility to FDA's ability to expedite development and approval of promising drugs, with the goal of increasing early access to these drugs for patients with serious conditions. FDASIA bolstered FDA's ability to review promising applications expeditiously through the creation of the "Breakthrough Therapy" designation, and by providing the FDA the ability to consider breakthrough-designated products for expedited priority review. FDASIA also added additional provisions to the accelerated approval program, including the ability to use an intermediate clinical endpoint seen earlier than irreversible morbidity or mortality. Changes to the expedited programs were clarified in a guidance to industry (6).

Our previous report (1) was an initial assessment of how and when the FDA was approving drugs in the advent of the then newly formed OODP and before FDAAA. The enactments of FDAAA and FDASIA, as well as the reorganization of OODP into OHOP, considerably changed the landscape of drug approval in oncology. These changes have allowed OHOP to be proactive in its response to the dramatic improvement in efficacy seen with many contemporary oncology drug and biologic products. Roberts et al. (7) also note that drug approvals actions are taken earlier by FDA compared to European Medicines Agency.

In light of the regulatory changes cited above, this article reviews new hematology oncology drug and biologic licensing applications and supplemental applications that were approved for new uses by OHOP between January 1, 2008 and December 31, 2016. The goal is to provide a detailed overview of the products approved by OHOP, and to summarize the changes in the laws, regulations, and the organization that occurred between 2008 and 2016; and to summarize the impact these changes had on regulatory drug approvals. We hypothesize that the FDA has made consistent use of regulatory mechanisms for expediting the approval of drugs over time. Therefore, the specific objectives of our project are to determine whether FDA has made consistent use of regulatory mechanisms for expediting the approval of drugs over time, to describe the kinds of clinical trials that supported the approval of these applications, and to help provide clarity about the context in which FDA makes use of such mechanisms.

Methods

Data and Information Sources

The primary sources for the data and information used in this review and analysis are the package insert and FDA records. This review covers new drug applications and biologic licensing applications and supplemental applications that were approved for new indications by OODP/OHOP between January 1, 2008 and December 31, 2016. As in our previous report (1), we exclude NDAs and BLAs involving medical imaging products, applications that were submitted for dosing and safety labeling revisions, and applications for topically applied dermatological oncology products. Products that are reviewed in the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health are also not included in this review.

Data Collected

Upon submission to OHOP, drugs can receive either standard review (10-month review cycle from time of filing) or priority review (6-month review cycle from time of filing). The requirements for being granted priority review are documented in the *Guidance for Industry: Expedited Programs for Serious Conditions: Drugs and Biologics* (6). In OHOP, priority review is most commonly granted for products that treat a serious condition and, if approved, would provide a marked improvement in safety or effectiveness.

Two types of FDA approvals exist for drugs or biological products: regular and accelerated. Regular approval requires that a drug or biological product demonstrate substantial evidence of clinical benefit or improvement in an established surrogate endpoint for clinical benefit. Accelerated approval was promulgated in 1992, primarily in response to the AIDS/HIV crisis, to provide an expedited method to approve drugs for patients who have serious or life-threatening diseases when these drugs show activity based on surrogate markers that are reasonably likely to predict clinical benefit above that of available therapies (7).

Applications that received priority review, type of approval granted, products that were new molecular entities (NMEs), and products approved that had previously received breakthrough designation for the indication approved were identified. In addition, we identified a single pivotal trial that was the primary basis for the approval. The pivotal trial was typically the trial completed directly before submission of the application. We captured the primary endpoint(s) used in each trial, as well as whether the trial utilized an interim analysis. As described elsewhere (1,8), the five most commonly used outcomes or endpoints to evaluate a new oncological drug product are overall survival (OS), disease-free survival (DFS), time to progression (TTP), progression-free survival (PFS), and objective response rate (ORR). In addition, we captured the sample sizes of all the trials supporting the efficacy of an application. Approvals of combination therapies were counted as a single application, even if multiple applications were submitted.

Results

OHOP approved drug products for 260 indications between 2008 and 2016. During this time period, OHOP issued a complete response to 27 applications, refused to file six applications, and 15 applications were withdrawn by the applicant. In addition, five indications were withdrawn for products that had previously received accelerated approval. The indications and reasons for their withdrawal are discussed in Beaver et al. (9). The approved indications were supported by 239 applications. Some of these applications supported approvals in more than one indication. For instance, filgrastim-sndz, the first approved biosimilar, received approval for indications in neutropenia, febrile neutropenia, and Acute myeloid leukemia (10). In contrast, two supplemental applications for pembrolizumab supported one indication in melanoma (11) (a conversion from an accelerated approval to a regular approval in 2015). Although OHOP also reviewed supplements to support updated labeling (eg, updated data for trials already described in the label), in this review, we focus only on the applications that resulted in the approval of a new indication during 2008–2016.

Figures 1–3 include data from 2006 and 2007 allowing comparisons of the data with respect to the regulatory changes described above. The number of approvals has trended upward in the subsequent years (Figure 1). Of the 239 applications reviewed, 141 (58.9%) were approved via priority review and 98 (41.0%) were approved via standard review. This is consistent with the findings of our previous review (1). There were 53 applications approved between July 1, 2005 and December 31, 2007, 39 received priority review (1). Taken together, we see that the FDA has given priority review to 61.6% of approvals since mid-2005. A large proportion of approvals were supplements in 2016, due to some therapies being studied in multiple diseases and lines of therapy. For instance, nivolumab, initially approved in 2014 (12), was approved for four new indications in 2016 for treatment of squamous cell carcinoma of the head and neck, non-small cell lung cancer (NSCLC), renal cell carcinoma, and classical Hodgkin's lymphoma (CHL) (13).

During 2008–2016, 53 (22.2%) of applications were granted accelerated approval, 29 (12.1%) were converted from accelerated approval to regular approval, and 157 (65.7%) received regular approval. Recently, there has been an increase in the number of applications verifying the clinical benefit of a previous accelerated approval indication through improvement in OS, PFS, or another clinical endpoint (Figure 2). Fulfilling the postmarketing requirement of an accelerated approval is depicted in Figure 2 as a "conversion" to a regular approval (Conv). Verification of benefit (Conv) occurred in eight applications in indications that had previously received accelerated approval in 2015, and for five applications in 2016.

An application was said to support a NME if at least one of the products approved in the application was an NME. Between 13.3% and 46.7% of applications approved each year were for NMEs (Figure 3). Kinch (14) noted the average number of NMEs in cancer has been increasing since 1951. Kinch estimates that the annual average number of approved NMEs was less than 2 per year before 1991, and between 4 and 5 during 1991–2010. From 2011 to 2016, we found that an average of 10.5 (63 overall) NMEs were approved each year. Novel therapies may also come in the form of combination therapies. The number of applications approved for combination therapies increased during 2008–2016: 1–4 combination therapies were approved each year during the first four years of this period, and 7–13 combinations were approved each year during the last four years of the period.

Since its promulgation in 2013, the breakthrough therapy designation has been applied to 25.7% of drugs that have ultimately received approval. The designation was granted to 8.7% (2/23) of approvals in 2013, the year it was introduced. The percentage of approvals granted breakthrough therapy designation rose in the subsequent years: 23.5% (8/34) in 2014, 26.7% (12/45) in 2015, and 38.2% (13/34) in 2016.

Mechanisms for expedited approval are not mutually exclusive, and are often used in conjunction. For instance, since 2013, all 35 applications receiving breakthrough therapy designation received priority review, compared with 56 of 101 (55.4%) applications not receiving breakthrough therapy designation. Similarly, 20 of the 35 (57.1%) breakthrough therapy–designated drug applications received either accelerated approval or were converted from accelerated approval to regular approval. Among applications not receiving breakthrough therapy designation, 30/101 (29.7%) were granted accelerated approval or converted from accelerated approval to regular approval.

During 2008–2016, the study sample sizes of the trials supporting the applications ranged from six patients for the use of methylene blue, which is indicated for the treatment of acquired methemoglobinemia (15), to 8292 patients for the use of edoxaban, which is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5–10 days of initial therapy with a parenteral anticoagulant (16). The median sample size for studies supporting the applications for approval was 345 patients. Similar to our previous study (1), we find that about a quarter of approved applications were supported primarily by a single-arm trial (60/239).

PFS and ORR (including complete response, objective response rate, pathological complete response, major molecular response, cytogenic response, etc.) were the most common endpoints used to support approval in the 2008–2016 time frame (Figure 4). These two endpoints were the primary endpoint in 83.0% of accelerated approvals (8 used PFS, 36 used ORR), and 57.0% of regular approvals or conversions to regular approval (59 used PFS, 47 used ORR). Applications approved based on these endpoints have increased slightly over time, with 55.3% of approved applications using these endpoints during 2006–2008 and 64.1% of applications using them during 2014–2016. Applications receiving regular approval when the pivotal trial was based on ORR or PFS included the approval of bevacizumab (2009) in combination with interferon (IFN)-α2a for the treatment of metastatic renal cell carcinoma, cabozantinib (2012) for the treatment of metastatic medullary thyroid cancer, and obinutuzumab (2013) in combination with chlorambucil for the treatment of Chronic lymphocytic leukemia.

Because PFS and ORR are much earlier events than death in the natural history of malignancy, trials using these endpoints can be performed with smaller sample sizes (8). The median sample size for trials used in approval are 656 patients for OS, 423 for PFS, and 140 for ORR. The dramatically smaller sample sizes for trials using ORR as the primary endpoint are not surprising, as these trials are usually single-arm studies. As noted above, 60 of the 239 (25.1%) applications approved were supported primarily by single-arm studies. Although not all single-arm studies reviewed used ORR as the primary endpoint, they all used an endpoint that was not a time-to-event endpoint as the primary endpoint, as time-to-event endpoint cannot be adequately characterized in a single-arm trial (8). Among the 60 approvals supported primarily by a single-arm trial, 28 (46.6%) were accelerated approval, 7 (11.7%) were postmarketing trials to verify benefit (a "conversion" of an accelerated approval to regular approval), and 25 (41.6%) supported regular approval. For comparison, of the 179 approvals supported by at least one randomized study, 25 (13.9%) supported accelerated approval, 22 (12.3%) supported a conversion from accelerated approval to regular approval, and 132 (73.7%) supported regular approval.

The proportion of studies using interim analysis has increased slightly since 2008, with 15/73 (20.5%) of studies employing interim analysis before 2012 and 43/166 (25.9%) of studies after 2012 (Figure 5). Of the 59 applications that contained an interim analysis, 34 (57.6%) were approved based on an interim efficacy analysis.

Figure 6 shows the number of indications approved by disease. There were 30 indications that were only approved in one disease and denoted as "Other"; these indications are detailed in Table 1. Table 2 shows all products approved during 2008–2016, as well as the disease of each indication for which each product was approved. The disease categories presented in Table 2 are more granular than in Figure 6, reflecting biomarker and histological heterogeneity within a disease.

Some of the diseases with only one approval from 2008–2016 are rare diseases. For instance, the disease with the

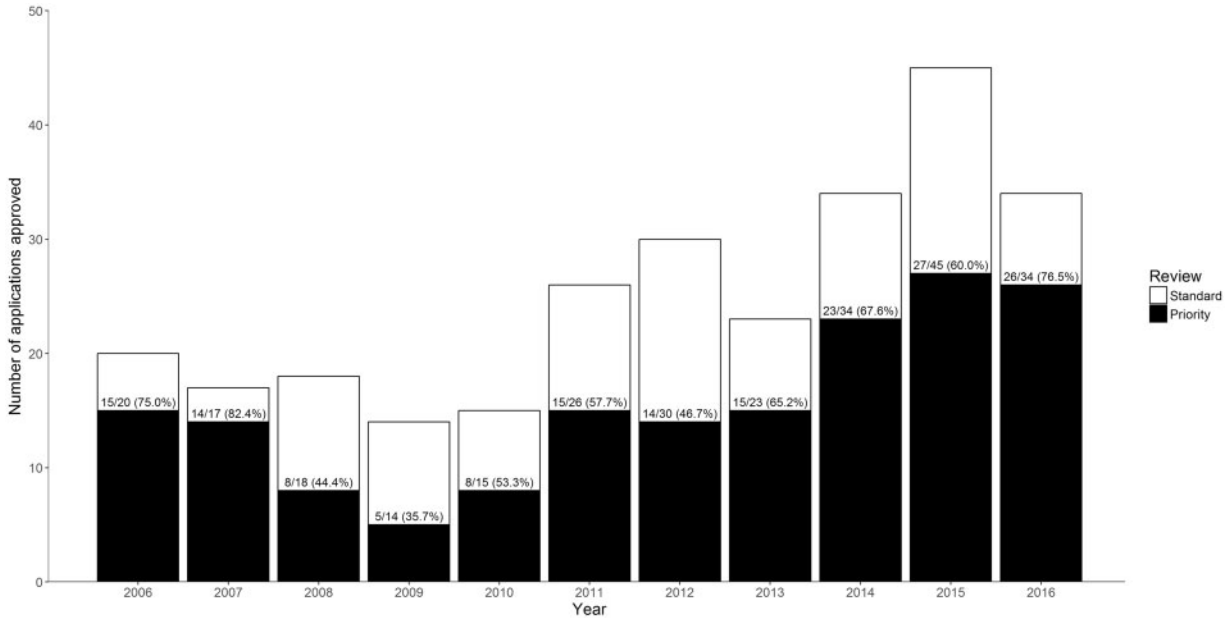

Figure 1. Number of approved applications by review type. The number of applications approved for a new indication in an oncology product by the US Food and Drug Administration (FDA) during 2006–2016, grouped by type of review. Approved applications receiving priority review (**Priority**), and those receiving standard review (**Standard**). The observed number and proportion of approved applications receiving priority review in each year are shown above the bar. Data used were taken from the package inserts of the approved products and FDA records.

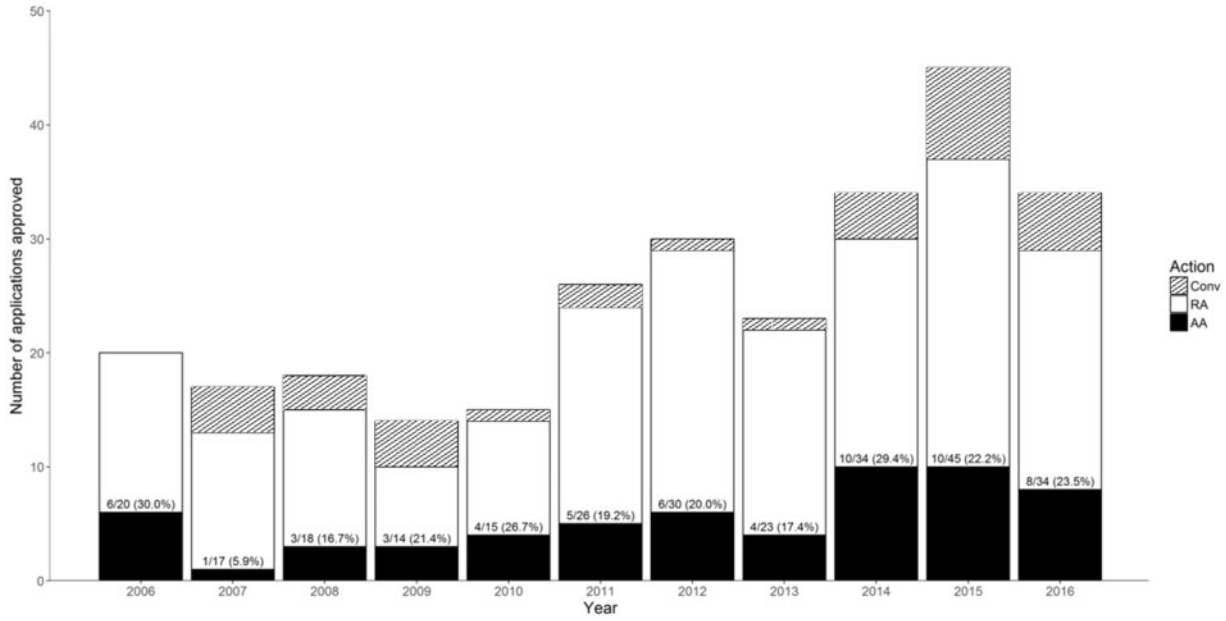

Figure 2. Number of approved applications by approval type. The number of applications approved for a new indication in an oncology product by the US Food and Drug Administration (FDA) during 2006–2016, grouped by type of approval type. Applications approved under accelerated approval (**AA**), applications approved under regular approval (**RA**), and applications which were converted from an accelerated approval to a regular approval (**Conv**) are shown. The observed number and proportion of applications approved under accelerated approval in each year are shown above the bar. Data used were taken from the package inserts of the approved products and FDA records.

fewest total number of subjects studied is atypical hemolytic uremic syndrome (aHUS), an extremely rare disease estimated to affect about 300 people living in the United States. In addition, multicentric Castleman's disease (MCD) is a rare disease of lymph nodes and related tissues for which prevalence and incidence is unknown (17,18). The results of the first-ever randomized clinical trial for Castleman's disease were published in 2014 (19) and siltuximab was approved for MCD that same year.

The time to approval has generally decreased since 2008. The time from the filing date to the approval date depends on a number of factors, such as the type of review (priority vs standard), NME status (the PDUFA review clock begins 60 days after the filing date for NMEs), and whether a three-month extension

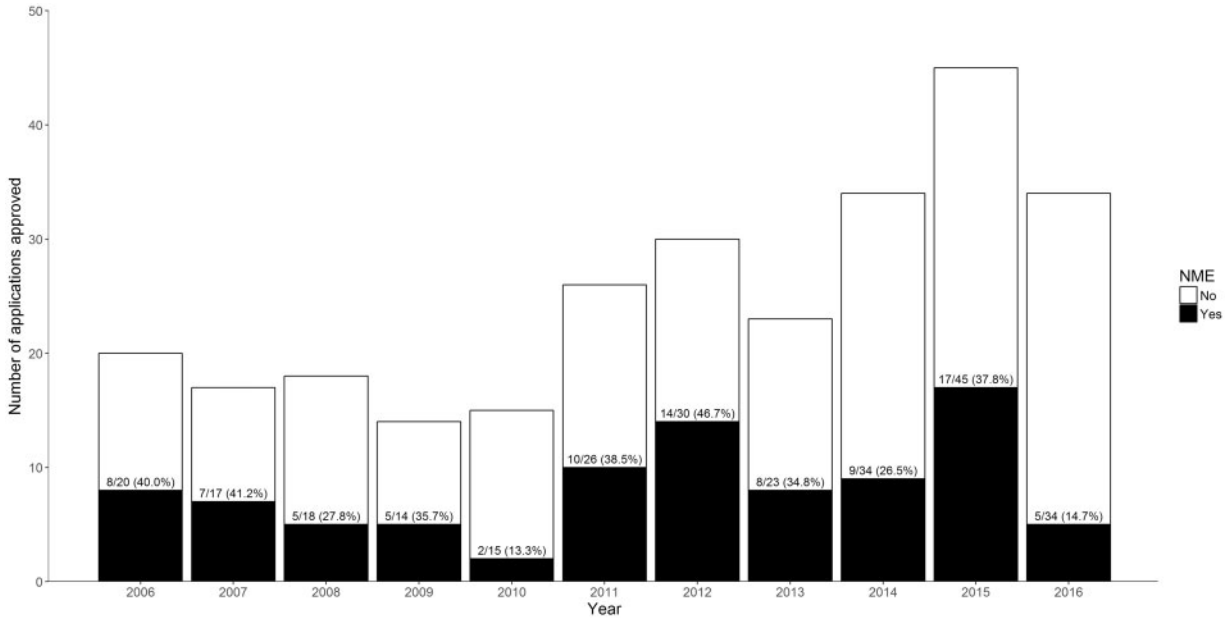

Figure 3. Number of approved applications by new molecular entity (NME) status. The number of applications approved for a new indication in an oncology product by the US Food and Drug Administration (FDA) during 2006–2016, grouped by whether at least one of the products was a NME or not. Approved applications for products that were NMEs (**Yes**) and those for products that were not NMEs (**No**) are shown. The observed number and proportion of approved applications for products that were NMEs in each year are shown above the bar. Data used were taken from the package inserts of the approved products and FDA records.

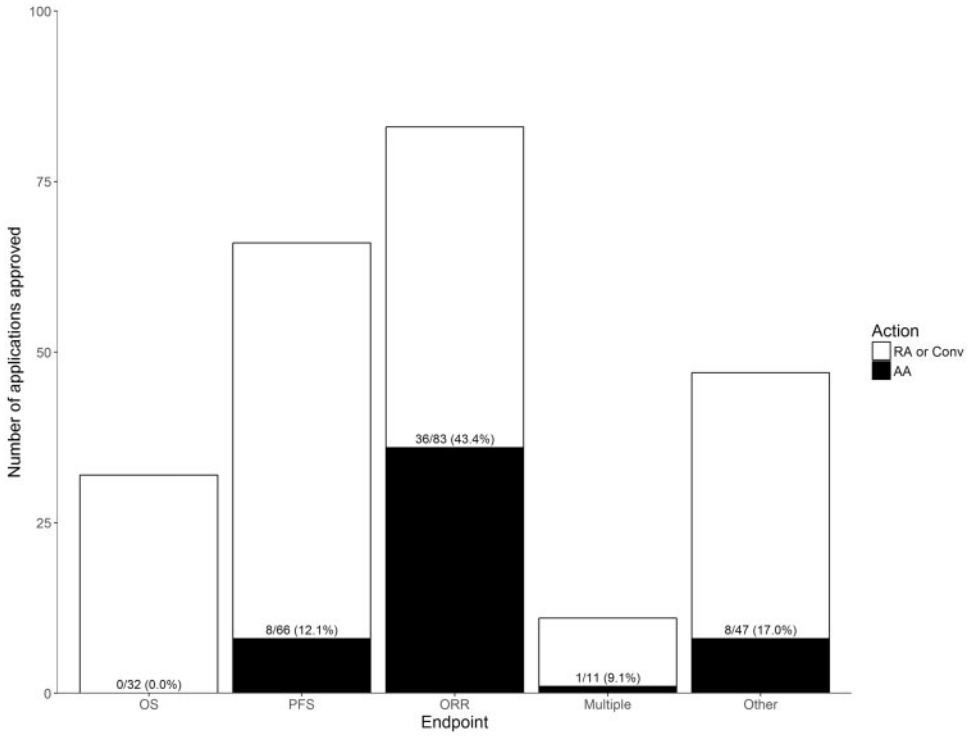

Figure 4. Number of applications approved by endpoint. The number of applications approved for a new indication in an oncology product by the US Food and Drug Administration (FDA) during 2008–2016, grouped by primary endpoint of the trial that supported the application. Endpoints are abbreviated as follows: overall survival (**OS**), progression free survival (**PFS**), objective response rate (**ORR**), relapse-free survival (**RFS**), event-free survival (**EFS**), multiple endpoints other than a coprimary endpoint of overall survival and progression-free survival (**Multiple**), and other endpoints not included in the previous categories (**Other**). Types of approvals are abbreviated as follows: regular approval (**RA**), conversion to regular approval (**Conv**), and accelerated approval (**AA**). Data used were taken from the package inserts of the approved products and FDA records.

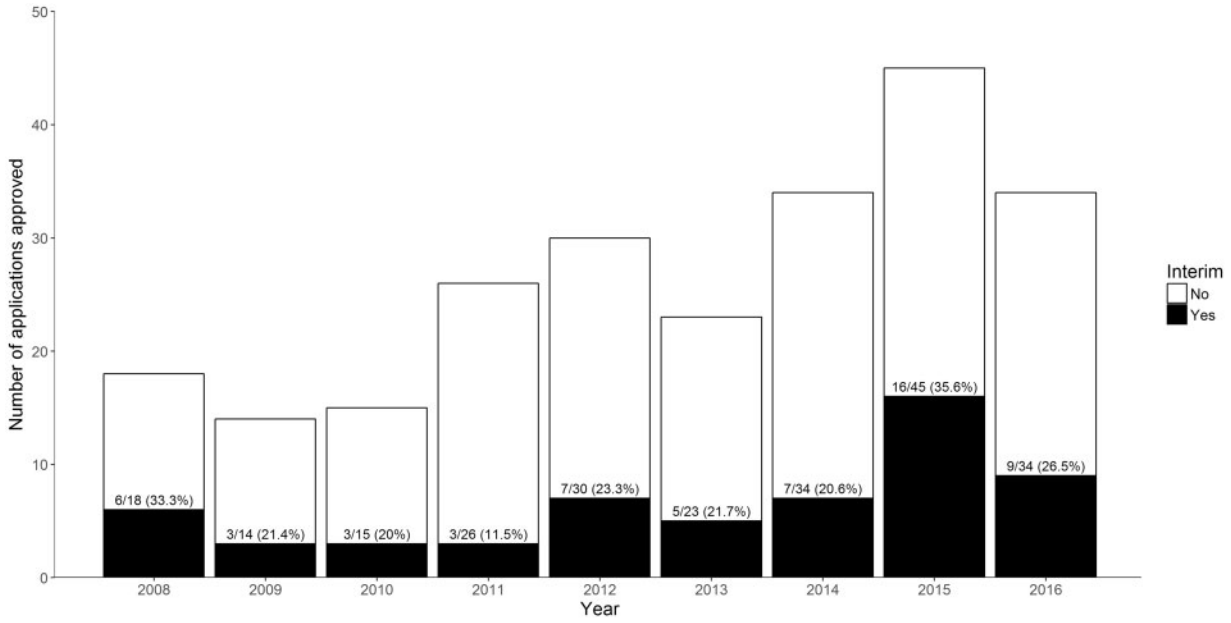

Figure 5. Number of approved applications by use of interim analysis. The number of applications approved for a new indication in an oncology product by the US Food and Drug Administration (FDA) during 2008–2016, grouped by whether the trial supporting the application used an interim analysis. Approved applications that were supported by a trial utilizing an interim analysis (**Yes**), and those that were supported by a trial not utilizing an interim analysis (**No**). The observed number and proportion of approved applications supported by a trial using interim analysis in each year are shown above the bar. Data used were taken from the package inserts of the approved products and FDA records.

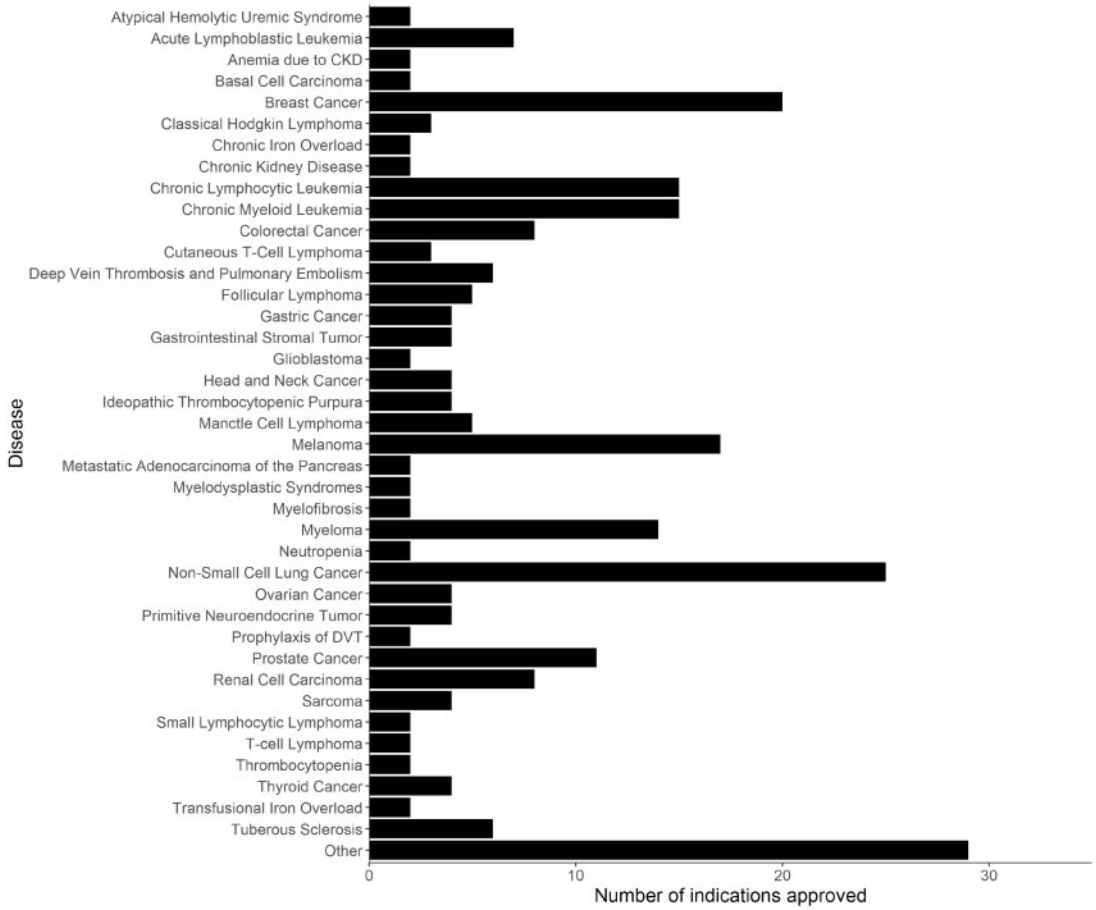

Figure 6. Number of approvals by disease. The number of new indications approved in oncology products by US Food and Drug Administration (FDA) during 2008–2016.

Table 1. Indications with only one approval during 2008–2016

Indication	Year	Name
Levoleucovorin rescue is indicated after high-dose methotrexate therapy in osteosarcoma.	2008	levoleucovorin
To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.	2008	levoleucovorin
Indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.	2008	bendamustine hydrochloride
In combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.	2008	plerixafor
After failure of prior systemic chemotherapy or intolerance to such therapy.	2008	doxorubicin
For initial management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.	2009	rasburicase
Refractory anaplastic astrocytoma, patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.	2009	temozolomide
Prevention of skeletal-related events in patients with bone metastases from solid tumors.	2010	denosumab
Toxic plasma methotrexate concentrations due to impaired renal function	2012	glucarpidase
Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity	2013	denosumab
For the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron or who have non–dialysis-dependent chronic kidney disease.	2013	ferric carboxymaltose
Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.	2014	bevacizumab
Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.	2014	denosumab
For the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.	2014	siltuximab
Polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.	2014	ruxolitinib
The treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).	2014	lanreotide
Patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.	2014	eltrombopag
In combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-*cis*-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.	2015	dinutuximab
Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia.	2015	filgrastim-sndz
Reduce the duration of neutropenia and neutropenia-related clinical sequelae, eg, febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation.	2015	filgrastim-sndz
In patients treated with idarcizumab when reversal of the anticoagulant effects of dabigatran is needed: for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding.	2015	idarucizumab
Waldenström's macroglobulinemia.	2015	ibrutinib
For the emergency treatment of adult and pediatric patients: following a fluorouracil or capecitabine overdose regardless of the presence of symptoms, or who exhibit early-onset, severe or life-threatening toxicity affecting the cardiac or central nervous system, and/or early-onset, unusually severe adverse reactions (eg, gastrointestinal toxicity and/or neutropenia) within 96 h following the end of fluorouracil or capecitabine administration.	2015	uridine triacetate
For the treatment of hereditary orotic aciduria.	2015	uridine triacetate
For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.	2016	atezolizumab
For the treatment of pediatric and adult patients with acquired methemoglobinemia.	2016	methylene blue
High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.	2016	melphalan hydrochloride
Adult and pediatric patients with hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation (HSCT).	2016	defibrotide sodium

Table 2. Products approved during 2008–2016, sorted by disease of indication approved

Disease and subgroup	Products (year indication of product was approved)
Anemia due to chronic kidney disease	ferumoxytol (2009), peginesatide (2012)
Chronic iron overload	deferasirox (2013), deferasirox (2015)
Chronic kidney disease	iron sucrose (2012)
Hemodialysis-dependent chronic kidney disease	ferric pyrophosphate citrate (2015)
Deep vein thrombosis and pulmonary embolism	rivaroxaban (2012), rivaroxaban (2012), rivaroxaban (2012), apixaban (2014), dabigatran etexilate mesylate (2014), edoxaban tosylate (2015)
Ideopathic thrombocytopenic purpura	romiplostim (2008), eltrombopag (2008), eltrombopag (2015), eltrombopag (2015)
Prophylaxis of deep vein yhrombosis	rivaroxaban (2011), dabigatran etexilate mesylate (2015)
Thrombocytopenia	eltrombopag (2011), eltrombopag (2012)
Other benign hematological diseases*	deferiprone (2011), ferric carboxymaltose (2013), eltrombopag (2014), deferiprone (2015), defibrotide sodium (2016)
Atypical hemolytic uremic syndrome	eculizumab (2011), eculizumab (2014)
Acute lymphoblastic leukemia	asparaginase Erwinia chrysanthemi (2011), asparaginase Erwinia chrysanthemi (2014)
Ph−	vinCRIStine sulfate LIPOSOME (2012)
Ph+	ponatinib (2012), imatinib mesylate (2013), blinatumomab (2014)
T315I+, Ph+	ponatinib (2016)
Classical Hodgkin's lymphoma	brentuximab vedotin (2011), brentuximab vedotin (2015), nivolumab (2016)
Chronic lymphocytic leukemia	bendamustine hydrochloride (2008), ofatumumab (2009), obinutuzumab (2013), ofatumumab (2014), ibrutinib (2014), ibrutinib (2014), idelalisib (2014), ofatumumab (2016), ofatumumab (2016), ibrutinib (2016), ibrutinib (2016)
17p deletion	venetoclax (2016)
B-cell	fludarabine phosphate (2008)
CD20+	rituximab (2010), rituximab (2010)
Chronic myeloid leukemia	nilotinib (2010), nilotinib (2010), ponatinib (2012), omacetaxine mepesuccinate (2012), omacetaxine mepesuccinate (2014)
Ph+	imatinib mesylate (2009), dasatinib (2009), dasatinib (2010), imatinib mesylate (2011), nilotinib (2011), bosutinib (2012), nilotinib (2012), dasatinib (2015), nilotinib (2015)
T315I+	ponatinib (2016)
Cutaneous T-cell lymphoma	romidepsin (2009), nitrogen mustard (2013)
CD25 expressing	denileukin diftitox (2008)
Follicular lymphoma	ibritumomab tiuxetan (2009), rituximab (2011), rituximab (2012), idelalisib (2014), obinutuzumab (2016)
Mantle cell lymphoma	ibrutinib (2013), lenalidomide (2013), bortezomib (2014), bortezomib (2014), lenalidomide (2015)
Myelodysplatic syndrome	decitabine (2010), decitabine (2014)
Myelofibrosis	ruxolitinib (2011), ruxolitinib phosphate (2013)
Myeloma	bortezomib (2008), bortezomib (2011), carfilzomib (2012), bortezomib (2012), pomalidomide (2013), elotuzumab (2015), daratumumab (2015), carfilzomib (2015), pomalidomide (2015), panobinostat (2015), ixazomib (2015), daratumumab (2016), carfilzomib (2016), melphalan hydrochloride (2016)
Small lymphocytic lymphoma	Idelalisib (2014), ibrutinib (2016)
T-cell lymphoma	romidepsin (2011), belinostat (2014)
Peripheral	pralatrexate (2009)
Other malignant hematological diseases	bendamustine hydrochloride (2008), plerixafor (2008), denosumab (2014), siltuximab (2014), ruxolitinib (2014), ibrutinib (2015)
Basal cell	vismodegib (2012), sonidegib (2015)
Breast cancer	bevacizumab (2008), eribulin mesylate (2010), letrozole (2010), denosumab (2011), anastrozole (2011), ixabepilone (2011), pertuzumab (2013), pertuzumab (2015), palbociclib (2016)
ER+	lapatinib (2010)
ER+, HER2−	everolimus (2012), palbociclib (2015)
HER2−	bevacizumab (2008)
HER2+	trastuzumab (2008), trastuzumab (2008), letrozole (2010), fulvestrant (2010), pertuzumab (2012), pertuzumab (2013), ado-trastuzumab emtansine (2013)
Colorectal cancer	levoleucovorin (2011), ziv-afilbercept (2012), regorafenib (2012), bevacizumab (2013), ramucirumab (2015), trifluridine and tipiracil (2015)
KRAS wild-type	panitumumab (2014)
KRAS wild-type, EGFR expressing	cetuximab (2012)
Gastric cancer	ramucirumab (2014), ramucirumab (2014), docetaxel (2014)
HER2-overexpressing	trastuzumab (2010)

(continued)

Table 2. (continued)

Disease and subgroup	Products (year indication of product was approved)
Gastrointestinal stromal tumor	imatinib mesylate (2008), imatinib mesylate (2008), regorafenib (2013)
Kit	imatinib mesylate (2012)
Glioblastoma	bevacizumab (2009), temozolomide (2009)
Head and neck cancer	cetuximab (2011), docetaxel (2014), pembrolizumab (2016), nivolumab (2016)
Melanoma	peginterferon alfa-2b (2011), ipilimumab (2011), pembrolizumab (2014), nivolumab (2014), ipilimumab (2015), pembrolizumab (2015), nivolumab (2015), nivolumab (2016), nivolumab (2016)
BRAF V600 wild-type	nivolumab (2015)
BRAF V600E	vemurafenib (2011), dabrafenib (2013)
BRAF V600E or V600K	trametinib (2013), dabrafenib (2014), trametinib (2014), dabrafenib (2015), cobimetinib (2015)
Metastatic adenocarcinoma of the pancreas	paclitaxel (2013), irinotecan liposome (2015)
Non-small cell lung cancer	pemetrexed disodium (2008), pemetrexed disodium (2009), erlotinib (2010), pemetrexed (2012), paclitaxel (2012), ramucirumab (2014), nivolumab (2016), atezolizumab (2016), afatinib (2016)
ALK+	crizotinib (2011), crizotinib (2013), ceritinib (2014), alectinib (2015)
EGFR exon 19 deletions or exon 21 (L858R) substitution mutations	erlotinib hydrochloride (2008), afatinib (2013), erlotinib (2013), gefitinib (2015)
EGFR T790M+	osimertinib (2015)
PD-L1 expressing	pembrolizumab (2015), pembrolizumab (2016)
PD-L1 high	pembrolizumab (2016)
ROS1+	crizotinib (2016)
Squamous	nivolumab (2015), necitumumab (2015), nivolumab (2015)
Ovarian	bevacizumab (2014), bevacizumab (2016)
Deleterious BRCA mutation	olaparib (2014), rucaparib (2016)
Primitive neuroendocrine Tumor	sunitinib malate (2011), everolimus (2011), everolimus (2011), everolimus (2016)
Prostate	degarelix (2008), cabazitaxel (2010), triptorelin pamoate (2010), denosumab (2011), abiraterone acetate (2011), leuprolide acetate (2011), abiraterone acetate (2012), enzalutamide (2012), radium Ra 223 dichloride (2013), enzalutamide (2014), enzalutamide (2016)
Renal cell	bevacizumab (2009), everolimus (2009), pazopanib (2009), axitinib (2012), nivolumab (2015), nivolumab (2016), lenvatinib (2016), cabozantinib (2016)
Sarcoma	pazopanib (2012), trabectedin (2015), olaratumab (2016), eribulin mesylate (2016)
Thyroid	sorafenib tosylate (2013), lenvatinib (2015)
Medullary	vandetanib (2011), cabozantinib (2012)
Tumor-induced osteomalacia	deferiprone (2015)
Due to thealassemia syndromes	deferiprone (2011)
Tuberous sclerosis	everolimus (2012), everolimus (2012), everolimus (2016), everolimus (2016), everolimus (2016)
Subependymal giant cell astrocytoma	everolimus (2010)
Other nonhematological diseases*	levoleucovorin (2008), doxorubicin (2008), temozolomide (2009), denosumab (2010), everolimus (2010), denosumab (2013), bevacizumab (2014), lanreotide (2014), dinutuximab (2015), atezolizumab (2016)
Neutropenia	tbo-filgrastim (2012), filgrastim-sndz (2015)
Other diseases*	levoleucovorin (2008), rasburicase (2009), glucarpidase (2012), filgrastim-sndz (2015), filgrastim-sndz (2015), idarucizumab (2015), uridine triacetate (2015), uridine triacetate (2015), methylene blue (2016), melphalan hydrochloride (2016)

*Indications are detailed in Table 1.

to the PDUFA goal date is needed due to major amendments. For applications that did not need a three-month extension, the median time from filing to approval decrease from eight months in 2008 to four months in 2016. A more direct measure of the change in time to approval during 2008–2016 is the time from the approval date to the PDUFA date. The percentage of applications approved at least four weeks early has risen from 0.0% in 2008 to 28.1% in 2016. This increase is true also for applications approved at least eight weeks early. In fact, in 2015 and 2016, most applications that were approved at least four weeks early were approved at least eight weeks early. Finally, the average percentage of the PDUFA review clock used has decreased from 102.6% in 2008 to 82.4% in 2016.

Discussion

The FDA approved 239 oncology and hematology marketing applications between January 1, 2008 and December 31, 2016, supporting the approval of 260 indications. Fifty-three (22.2%) of these applications were granted accelerated approval, 29 (12.1%) were converted from accelerated approval to regular approval, and 157 (65.7%) received regular approval. Furthermore, 141 (58.9%) of these were designated for priority review. Since its promulgation in 2013, the breakthrough designation has been granted to 25.7% of applications approved by OODP/OHOP; all of these therapies received priority review, further expediting their development and approval.

Our results suggest that FDA has made consistent use of regulatory mechanisms to expedite approvals over time. There seems to be no discernable trend in percentage of applications granted priority review or accelerated approval over time. The decision to grant either of these expedited pathways depends on the totality of evidence, severity of disease, available treatments, current understanding of surrogate endpoints, and a balancing of benefit vs risk. The availability of new molecular entities (NMEs) also does not seem to have a discernable trend, as evidenced by the number of approved applications supporting NMEs over time. However, novel therapies are not limited to NMEs, and include novel combinations, which have risen in the past few years.

Our study is limited to oncology and hematology products, and may not be indicative of FDA's actions in other disease areas. Additionally, there is significant heterogeneity among the diseases reported here, resulting in different endpoints that may be appropriate for different diseases, different sample sizes necessary to show benefit, etc. This report does not address what endpoints may be appropriate for a particular disease, whether accelerated approval would be likely for a given surrogate endpoint in a particular disease, or what sample size might be appropriate for a clinical trial in a particular disease. Lastly, this report only considers the primary endpoints of the trial used to support approval of an application. The approval of an application depends on many other factors which may affect the risk–benefit assessment of the product in question, such as safety, tolerability, secondary endpoints, etc.

This article provides an overview of the regulatory actions OODP/OHOP has taken during 2008–2016. This is a larger time window than our previous report (1) and consequently allows for the exploration of trends and consistencies in drug approval during this time. For instance, the use of interim analysis seems to be increasing. There is also a continued robust use of accelerated approval and other expedited programs including the more recent breakthrough therapy designation. FDA's Office of Hematology and Oncology Products remains committed to the thoughtful use of expedited programs and efficient review practices to hasten the delivery of safe and effective anti-cancer drugs to the American public. Many of the findings presented here demonstrate the FDA's consistency in using regulatory mechanisms over time. For instance, the FDA's use of accelerated approval has been relatively constant since 2008. Although use of these mechanisms depends on the kinds of applications submitted to the agency in each year, the data presented here portray a broad picture of consistent use of regulatory mechanisms by both the sponsor and the FDA. The frequency of use of these mechanisms and of approving applications based on various endpoints demonstrates the FDA's commitment to utilizing such flexibility when making decisions about treatments for serious or life-threatening diseases.

Note

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