FDA's Accelerated Approval Process: Efficacy Assessment of Surrogate Endpoints And Post-Marketing Studies

by

Saikavya Bekal Rao

Research Project

Submitted to the College of Health and Human Services

Eastern Michigan University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Clinical Research Administration

Prof. Irwin Martin

11/17/18

Ypsilanti, Michigan

Abstract

The Food and Drug Administration's Accelerated Approval process was an initiative that was undertaken in 1992 to aid in faster approval of drugs that are intended to treat serious or life threatening conditions for which there were no satisfactory treatments available. These drugs are granted accelerated approval status based on the efficacy of surrogate endpoints which would likely correlate with the clinical benefit of a drug. Sponsors are required to conduct post-marketing studies under the provision of accelerated approval to prove the clinical benefit of such products. Even though such drugs have been in the market for a long time, there are controversies surrounding the use of surrogate endpoints and the approval of drugs before they have proved their clinical efficacy. This project reviewed the drugs approved under the accelerated pathway between July 2008 and December 2017 and compared the status of the confirmatory post-marketing studies to an earlier report submitted by Government Accountability Office (GAO). Information on each drug and surrogate endpoint used was obtained by searching the FDA database and the status of the requested post-marketing studies were identified and classified. Of the 124 post-marketing studies requested for 82 applications, 56 (45.2%) were closed or completed and 68 (54.8%) are still open. In comparison to the results submitted by GAO, there is an 18.8 % increase in number of studies that are open, however a positive trend was seen in the completion of these studies. There is need to closely monitor the reliability of surrogate endpoints and regulate the confirmatory post-marketing studies stringently.

Table of Contents

List of Tables

List of Figures

Introduction and Background

FDA is responsible for reviewing and approving new drug applications (NDAs) and Biologics License application (BLA) based on whether or not the drug meets the safety and efficacy standards set for the intended disease population. In the traditional approval process of a drug or biologic, the sponsor conducts clinical trials to demonstrate proof of benefit compared to the product's risk profile. The best primary efficacy endpoints are chosen that reflect true clinical benefits to patients. This encompasses directly measuring how the patient feels and how functioning or survival is affected (FDA, 2018). Often times determining and selecting the true clinical efficacy endpoints poses the biggest challenge while designing the clinical trials. In conditions that are life threatening, one would like to see the efficacy on mortality or on quality of life that is clinically relevant. These may include alleviation of symptoms related to the disease, ease in performing activities of daily life or diminished hospital stay time. To prove that a drug can improve quality of life or survival rate in cancer patients, or to prove that a vaccine has the ability to decrease the spread of HIV, or to prove that a device has the potential to reduce cardiovascular outcomes will necessitate large scale clinical studies that are conducted for extensive periods of time (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009). From the time a drug is discovered until the time it is marketed, it undergoes several stages of testing, including the pre-clinical testing, clinical testing (Phase 1 to Phase 3) and NDA approval. It can take approximately 15 years for a drug to pass through all these stages (Independent Institute, 2018). According to the Independent Institute's assessment, prior to the enactment of the Accelerated Approval process in 1990s, a drug typically had to be tested

in over 60 clinical trials which involved about 5000 subjects. This would mean that the patients with serious or life threatening conditions would not have immediate access to new treatments. Such studies were very expensive to conduct (Fleming, 2005).

Wilson, Schenkein, Jernigan, Woodcock, and Schilsky (2013) stated that in 1980s, when the AIDS crisis emerged, the AIDS activists demanded that the speed of drug development be improved. According to them, since the first reported case of AIDS in 1981, a lot of people suffered from this debilitating condition. During the early 1980s, AIDS patients did not have any treatment options and there were many fatalities. Those who survived had very poor disease prognosis. Due to the increasing burden of the disease, they were willing to bear the risk of any clinical outcome of the drugs approved under the expedited pathway (Wilson et al., 2013). As an alternative to the traditional endpoints used in studies, the sponsors suggested the use of surrogate endpoints, which are biological markers that correspond to the clinical efficacy endpoint (NIH, 1996). They wanted to use this endpoint to measure the early and widespread effect of the experimental drug. A surrogate endpoint could be laboratory measurement, radiologic evidence, physical sign or any other measure that has the ability to predict the clinical benefits but does not measure the clinical benefit as such and patients who show better results to such surrogate endpoints were thought likely to have positive response to clinical efficacy endpoints (FDA, 2018). In response to this pressing need to develop faster drugs for HIV patients, FDA launched the Accelerated Approval regulatory pathway in 1992 that allowed the use of surrogate endpoints for regulatory approval (Wilson et al., 2013). Per this pathway, drugs were granted accelerated approval based on their efficacy on surrogate endpoints were thought to predict the clinical

benefits of a drug. In turn, FDA mandated the sponsors to conduct post-marketing studies within a certain timeframe to verify the relationship between the drug's effect on surrogate endpoint and the actual clinical outcomes (FDA, 2018). The post-marketing confirmatory studies must be in compliance with the Food and Drug Administration Modernization Act of 1997 (FDAMA) (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009). Per GAO, the sponsors seeking approval for their drugs under Accelerated Approval must communicate with the FDA regarding the potential of their drug, the proposed surrogate endpoints, the design of the clinical studies and the Phase 4 confirmatory studies at an earlier stage of drug development. HIVID (Zalcitabine) was the first drug approved under the accelerated process in 1992 by FDA to treat HIV. Since then, this approval pathway has been used primarily for developing drugs for conditions such as HIV/AIDS, oncology, acute disease conditions, and recently for influenza vaccines (Wilson et al., 2013). An example of surrogate endpoints is reduction in HIV viral load in the blood that has now been shown to reduce mortality and morbidity associated with HIV (Hull & Montaner, 2013). Also, reduction in tumor size as seen by radiographs has been shown to improve survival for certain type of cancers (Fleming, 2005). The overall aim of treating cancer patients is to extend their life span and to improve their quality of life. Based on that goal, disease-free survival has been used as accepted surrogate endpoint for overall survival in colon and breast cancer (Johnson et al., 2011). If the results of the studies are positive, the status of the drugs can be converted to regular approval. On the other hand, if the drugs fail to show their efficacy, they can be withdrawn from the market (FDA, 2018).

FDA's oversight of post-marketing studies

FDA is able to monitor the sponsor's progress in conducting the post-marketing studies through the Annual Safety Reports (ASRs). These reports include information and status of the required post-marketing studies that were requested at the time of approval. Sponsors are required to submit these within 60 days of NDA/BLA's approval anniversary date. FDA also maintains a database for the post-marketing requirements (PMR). This includes the list of drugs approved under the accelerated access process, the requested PMRs, their projected completion date, actual completion date and the current status. Based on the information provided in the ASRs, FDA updates this database. They are able to track which studies are not keeping up with the timeline and can ask the sponsor for updates (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009). The Post-marketing studies are primarily classified as "Open" or "Closed" by FDA.

The open studies are further classified as follows (FDA, 2016).

Pending: The study has not commenced but it does not qualify to be labeled as Delayed.

Ongoing: The study is progressing as per, or is ahead of, the original projected timeline. Until the submission of a final study report, FDA considers a study to be ongoing.

Delayed: The study is falling behind from its original projected schedule.

Terminated: The study was discontinued before completion and a final study report was not submitted by the sponsor.

Submitted: The study has either been completed or terminated by the sponsor and a final study report has been submitted to the FDA, however FDA has not yet informed the sponsor on the status of the commitment (whether it has been fulfilled or released)

Closed studies are further classified as

Fulfilled: Those requested studies that are complete and for which the sponsor has submitted the final study report. Per FDA's review, the study has satisfactorily met the requirement and sponsor has been notified of the same via written communication.

Released: Those studies that are no longer required to be completed because they are either not feasible to conduct or they will no longer yield useful information.

Review of Literature

The United States Government Accountability Office submitted a report on FDA's oversight of drugs approved on the basis of surrogate endpoints to the Ranking Member Committee on Finance, U.S Senate in September of 2009 (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009). This report included review of drugs approved based on surrogate endpoints under the accelerated approval process from 1992 through November 20, 2008. There were 90 applications submitted for approval under this process with an average of 5 applications per year. Thirty-eight (42.2%) of these applications were indicated to treat cancer. For these 90 applications, sponsors were required to conduct 144 post-marketing confirmatory studies. The majority of these studies were required for oncologic and HIV/AIDS drugs. The status of each of the 144 post-marketing confirmatory studies as defined by FDA were assessed and categorized.

According to GAO, 92 of the total studies (64 %) were closed, whereas 52 of the total studies (36 %) were in open status. The open studies were further classified into various statuses. Of the 92 closed studies, 73 (79%) had fulfilled the FDA requirements and 19 (21 %) were released from their requirements.

The status of the 52 open studies follows.

1. Ongoing- 17 (33%)
2. Submitted- 16 (31%)
3. Delayed- 10 (19 %)
4. Pending- 7 (13%)
5. Terminated- 2 (4%)

Per GAO's analysis of the time taken by the sponsor of the 73 studies, 48 (67.7%) studies were fulfilled in less than 5 years whereas 23 (32.3%) took more than 5 years to fulfill. Of the different types of studies, oncology trials in particular took longer to complete. The rationale for this being that oncology drugs under the accelerated pathway were generally approved based on single-arm trials conducted in small numbers of patients with aggressive tumors. The confirmatory studies, however, had to be randomized trials that compared the approved drug in depth with placebo or other active drugs. Sponsors had to design newer randomized controlled trials and recruit larger patient populations. A lot of patients were reluctant to participate in the trials since the drug had been approved under the accelerated process was available in the market. It was easier for the HIV confirmatory studies to be conducted because the sponsors had only to continue the study that initially led to the original approval of drug under the accelerated pathway. Sponsors did not have to design any

new randomized trials. The trials conducted to obtain accelerated approval for HIV drugs were typically 24 week randomized clinical trials and to fulfill the post-marketing requirements, the sponsors had to continue the same study for another 24 weeks with the same patients and endpoints (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009).

Based on GAO's analysis, the 52 open studies averaged just over 4 years. Majority of these studies (71%) were in open status for less than 5 years. The remaining 29% of the studies were open for more than 5 years, with some being open for more than 8 years.

Purpose and Objective(s) of the Study

Since 1992, many drugs have been approved by the FDA under the Accelerated Approval program. Due to this program, patients with serious and life threatening conditions have been able to gain faster access to drugs before the clinical outcomes of the drug have been available. Even though such drugs have been in the market for a long time, there are controversies surrounding the use of surrogate endpoints and the approval of these drugs before they have proved their clinical efficacy. Since there are no data to prove the clinical benefit of the drug at the time of approval, it is possible that the drugs may not provide any meaningful benefit when used in larger patient population, or even worse, it may prove to be harmful. This may happen if the chosen surrogate endpoint is not predictive of the actual clinical benefit or because the expected risks of the drug exceed its benefits, which might go unnoticed in the absence of long term studies (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009).

There have been concerns raised about FDA's dependence on surrogate endpoints and the way the post-marketing studies are regulated. There was a recent instance in which as Avastin (*bevacizumab)* was approved under the accelerated pathway and failed to demonstrate its efficacy for metastatic breast cancer during the post-marketing studies (Sasich & Sukkari, 2012). ProAmatine (*midodrine)* was granted accelerated approval in 1996 for orthostatic hypotension. FDA granted approval on the condition that the sponsor would conduct confirmatory studies. However, the sponsor company, Shire Development Inc., did not conduct the necessary trials to prove the efficacy of the drug. The drug continued to be on the market, even though the studies were not conducted (Dhruva & Redberg, 2010). These illustrations raise concerns about the clinical efficacy of other drugs approved based on surrogate endpoints. It also raises questions on a sponsor's commitment to proactively conduct the post-marketing studies and the agency's regulatory oversight. Therefore, the key questions being addressed in this study were: (1) Are the surrogate endpoints used for approval of drugs under the accelerated approval process reliable predictors of clinical outcome as based on the number of post-marketing studies being completed? (2) Are sponsors diligently conducting the post-marketing studies as agreed upon at the time of approval? The Government Accountability office (GAO) had submitted a report in 2009 on the status and analysis of the post-marketing studies conducted for drugs approved on the basis of surrogate endpoints for the time period 1992- November 20, 2008. The purpose of this project is to identify the applications approved by FDA under the accelerated pathway from July 2008 to December 2017 and the status of the post-marketing studies to understand how closely the surrogate endpoints relate to the clinical outcomes. The

findings of this study will be compared with the results submitted by GAO to understand if there is any improvement in the efficacy of the accelerated approval process.

Methods

To identify the drugs and biologics applications that were approved from July 2008 to December 2017 on the basis of surrogate endpoints under the accelerated approval process, FDA's database for post-marketing requirements was searched (FDA, 2013). The search retrieved results for the time period specified with the list of post-marketing studies requested and their status. A spreadsheet was created to include the applicant's (sponsor) name, product name, indication, NDA/BLA number, and description of each post-marketing requirement including its current status, time from approval to current status, surrogate primary and secondary endpoints used for approval. Upon doing a public search, a PDF report by FDA was identified that provided a list of NDA and BLA accelerated approvals that were current as of June 30, 2018 (CDER, 2018). Some additional NDAs and BLAs that were not identified in the FDA's database for post-marketing requirements were able to be added to the spreadsheet.

To confirm the number and status of the post-marketing studies requested by FDA, each drug was searched separately on Drugs@FDA which provided the NDA/BLA application details (FDA, 2018). Upon clicking "Approval Date(s) and History, Letters, Labels, Reviews for NDA/BLA" further information on original application and any supplement applications were displayed. FDA letters corresponding to the approval date of the NDA/BLA were reviewed to see what post-marketing requirements were requested for the drugs under the Accelerated Approval process. These were verified against the data entered in the spreadsheet. If any additional requirements were identified in the letter, it was added to the spreadsheet. Next, FDA letters for each supplemental approval of the NDA/BLA was

reviewed to see if it stated “FULFILLMENT OF POSTMARKETING REQUIREMENT”. The letters with the information on fulfillment were searched to see which post-marketing requirements were fulfilled. If it matched the one required under the accelerated approval process it was verified against spreadsheet to identify the status and any missing information was updated. The date on which FDA issued the letter (action date) was used as date of fulfillment for the requirement. For some of the post-marketing studies whose status was unavailable, a public search was done to see if sponsors had any website where status of such studies was available. The following sponsor databases were identified: Novartis, Shire, GSK, BMS and MERCK. Full links to the databases are provided in the reference list. Also, https://clinicaltrials.gov/ website was searched to review the status of the post-marketing studies. The spreadsheet was updated according to the data retrieved.

The post-marketing studies were classified according to the following status and studies under each category were summed. Percentage of each category was then calculated.

- Delayed
- Pending
- Ongoing
- Terminated
- Submitted
- Fulfilled
- Released

The surrogate endpoints used were identified by reading through the medical review section of "Review" of original application and by looking at the label posted next to the NDA/BLA applications. Data from the spreadsheet were extracted to calculate the number of applications approved based on indications and the surrogate endpoints used, the number of post-marketing studies requested for each indication, the average time taken to fulfill the studies, and the age of the open studies. Studies under each category were summed and their percentages were calculated.

Results

The results on the status and analysis of the post-marketing studies conducted for drugs approved on the basis of surrogate endpoints for the time period 1992- November 20, 2008 are presented in the Government Accountability office's (GAO) report from 2009. Details are described in the literature review section. Since this study aims at updating the results with GAO's study, data from post July 2008 are presented in this section. Appendix A includes all the applications approved during the period July 1, 2008 to December 31, 2017 under the accelerated approval process. For each application, information on the drug name, NDA or BLA approval number, Accelerated Approval date, Approved indication, the surrogate endpoints as basis of approval, the number of post marketing studies requested and their statuses are provided.

Between the period of July 1, 2008 to December 31, 2017, a total of 82 applications were approved under the accelerated approval process. Of the 82 applications, 67 studies (81.7%) were oncology drugs. The rest of the 15 applications were for varied indications including spontaneous preterm birth, thalassemia syndrome, uncontrolled bleeding requiring emergency procedure, multidrug resistant tuberculosis, or iron overload. Highly specific surrogate endpoints were used as basis for approval for these drugs. A breakdown of the surrogate endpoints by indication is provided in Table 1. Some of the commonly used surrogate endpoints by several oncology drugs were progression free survival, overall survival, duration of response and tumor response rate.

Table 1: Summary of surrogate endpoints for Accelerated application approval, from July 2008 to Dec 2017.

Disease Type	Surrogate endpoints used for approval	Number of applications (Total 82)
Cancer	• Progression free survival • Response rate • Overall survival • Recurrence-free survival (RFS) • Time to progression • Best Confirmed Complete Cytogenetic Response (cCCyR) • Percentage of Participants With Major Molecular Response (MMR) at Any Time • Percentage of Participants With Objective Response (OR) • Angiomyolipoma Response Rate as Per Central Radiology Review • Major hematologic response • Response duration • Number of Participants Who Were Negative for Minimal Residual Disease (MRD)	67 (81.7%)
Preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.	• Percent of births occurring at <37 weeks gestation • Percent of births at <35 weeks at <32 weeks gestation • A composite index of neonatal morbidity and mortality	1

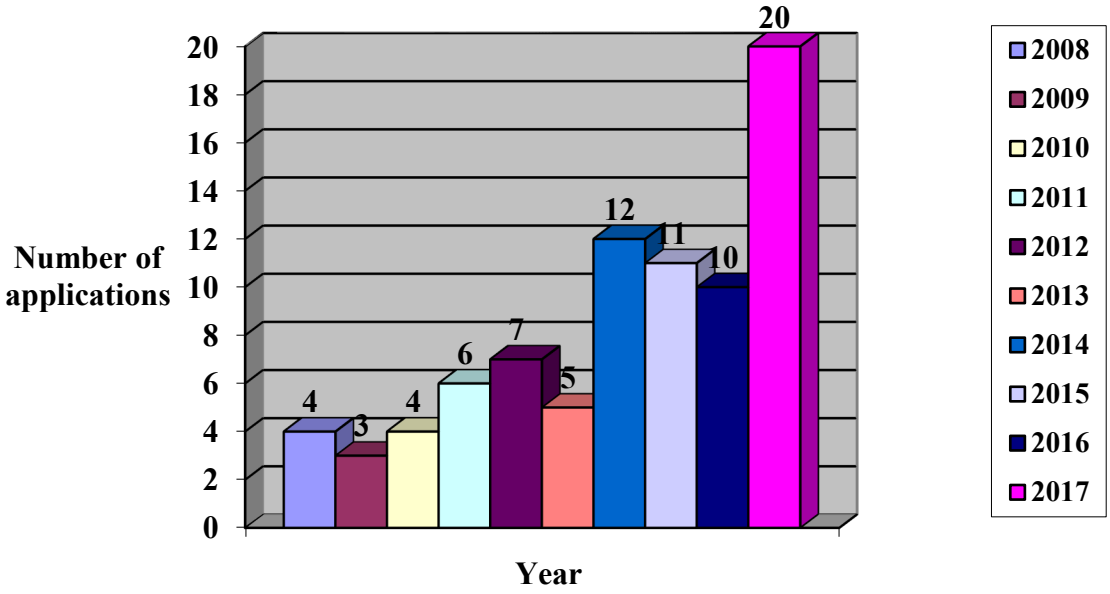
Disease Type	Surrogate endpoints used for approval	Number of applications (Total 82)
Iron overload in patients with sickle cell disease and transfusional iron overload due to thalassemia syndrome	• Serum ferritin levels • The change in Liver iron concentration after one year of treatment with deferiprone • measure changes in cardiac iron concentration • Measure liver iron concentration.	2
Uncontrolled Bleeding or Require Emergency Surgery or Procedures	• The maximum reversal of Ecarin (meizothrombin generation test used to accurately quantify direct thrombin inhibitors) Clotting Time or Dilute Thrombin Time in the first 4 hours was the primary endpoint • Decrease of unbound dabigatran to near undetectable concentration	1
sputum smear-positive pulmonary multidrug resistant tuberculosis	• Time to sputum culture conversion • Analysis of relapse • Time to culture conversion at Week 72 • Mortality rate	1
symptomatic neurogenic orthostatic hypotension	• The primary endpoint will be the mean change in ambulatory Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 from randomization to Week 4 of the randomized withdrawal period	1

Disease Type	Surrogate endpoints used for approval	Number of applications (Total 82)
Iron Overload	• Serum Ferritin • Liver Iron concentration	3
Chronic Immune (Idiopathic) Thrombocytopenia (ITP)	• Response rate defined as an increase from baseline platelet count to a count >= 50,000/mcl	1
Thalassemia Syndromes	• Serum Ferritin • Liver Iron concentration	1
Hunter Syndrome	• Change in urinary glycosaminoglycan (uGAG) levels • Minute walk test	1
Primary Biliary Cholangitis	• Reduction in alkaline phosphatase • gamma-glutamyl transferase (GGT) reduction • reduction of serum transaminase (ALT and AST).	1
Methemoglobinemia	• methemoglobin decrease of at least 50% at one hour after IV administration of ProvayBlue® Injection,	1
Duchenne Muscular Dystrophy	• increase in dystrophin	1

Disease Type	Surrogate endpoints used for approval	Number of applications (Total 82)
Chagas Disease	• reduction of conventional serology titers and conversion to negative of unconventional assays (immune responses to specific trypomastigote antigens F-29 and AT-ELISA	1

Based on the review of the number of accelerated applications approved per year between 2008- 2017, there are some ups and downs observed, however the trend is certainly positive. On an average, 8.2 applications were approved every year. The greatest number of applications was approved in 2017. Of the 20 drugs approved in that year, 18 were for oncology. The breakdown of the number of applications per year is shown in Figure 1.

Figure 1: Applications approved using surrogate endpoints under FDA's Accelerated Approval Process, July 2008- December 31, 2017



Of the 124 post-marketing studies requested for 82 applications, 56 (45.2%) were closed or completed and 68 (54.8%) are still in open status. Majority of the studies in open

state are the oncology clinical trials. The breakdown of the studies per status is shown in Table 2.

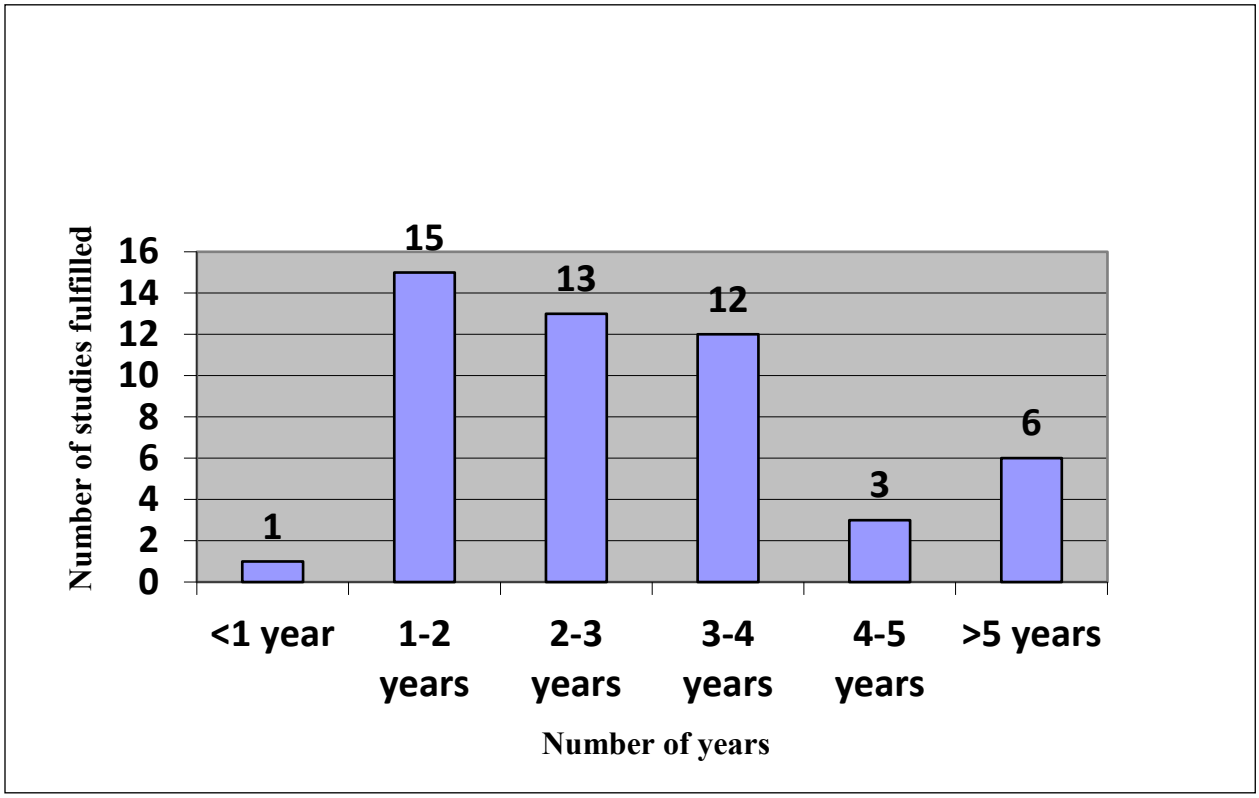
Table 2: Status of post-marketing studies requested under the accelerated approval process, from July 2008 to Dec 2017.

Status of open studies	**Number of studies (% of total)**
Pending	15 (22%)
Ongoing	34 (50%)
Delayed	11 (16.1%)
Terminated	3 (4.4%)
Submitted	5 (7.3%)
TOTAL OPEN	68 (54.8%)
Status of closed studies	**Number of studies (% of total)**
Fulfilled	50 (89.3%)
Released	6 (10.7%)
TOTAL CLOSED	56 (45.2%)
TOTAL STUDIES	124 (100%)

The time taken for the post-marketing studies to be fulfilled from the time of approval of the drugs under accelerated pathway was calculated. Per results of this study, 50 studies were fulfilled during the period July 1, 2008 – December 31, 2017. Of the 50 studies, sponsors were able to fulfill 44 (88 %) studies in less than 5 years whereas only 6 (12 %) studies took greater than 5 years to fulfill. The longest time taken from the time of drug

approval to fulfillment was 8.7 years and the shortest time taken was less than a year. The breakdown of time taken by studies to be fulfilled is shown in Figure 2.

Figure 2: Elapsed time from Drug approval to Fulfillment of Post-Marketing studies required under the Accelerated Approval Process, July 01, 2008- December 31, 2017.



For the 68 open studies, their age was calculated from the time of drug approval to the time of current status. According to the calculation of this study, average age of open studies (delayed, pending and ongoing) is roughly 3.21 years and majority has been open for

1-2 years. Twenty-three point five percent of studies have been open for more than 5 years. The breakdown is shown in figure 3.

Figure 3: The average age of open studies from the time of approval

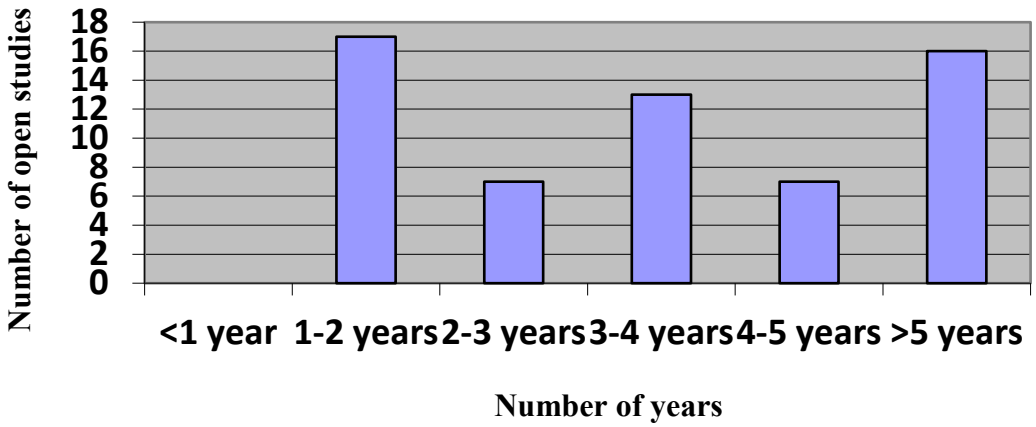
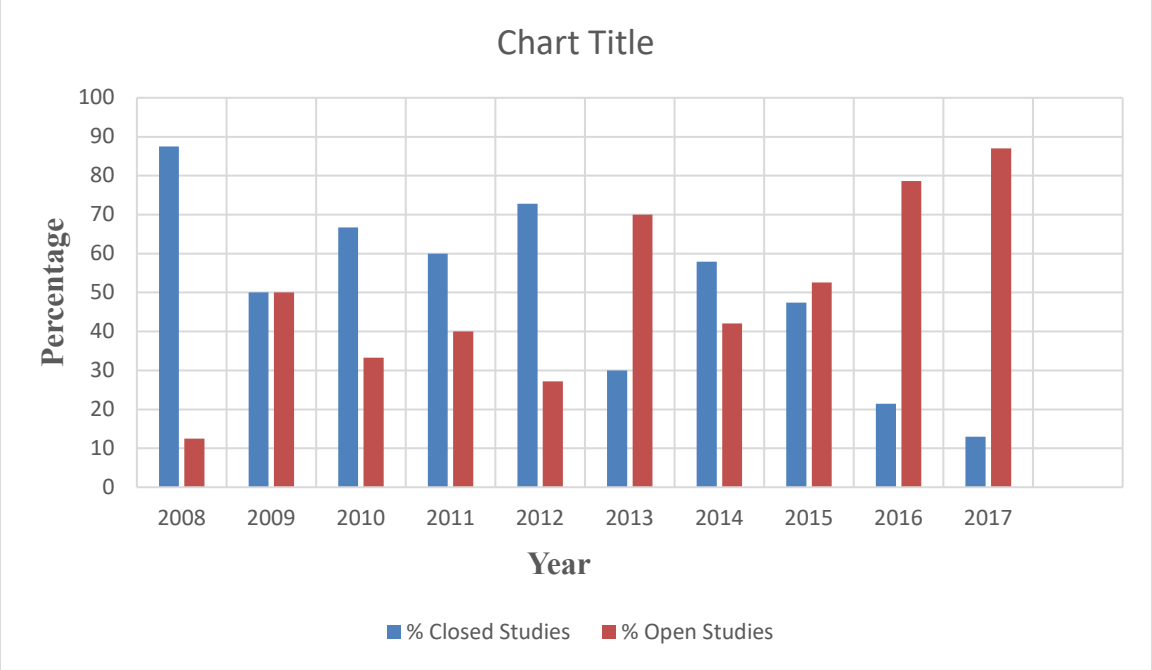


Figure 4 shows distribution of the percentages of the closed and open studies per year for the time period 2008- 2017. From 2008 to 2012, mostly a positive trend seen in the number of closed studies in comparison to the number of open studies. Only in 2009, the percentages were equal for both set of studies. Starting 2013, the numbers of open studies have remained higher than the number of closed studies except in the year 2014 which has more number of closed studies. This aligns closely with the observation made in Figure 3. The highest percentages of studies are from 2016 and 2017.

Figure 4: Percentage of closed and open studies per year from 2008- 2017



Failing to show clinical benefit, one application was withdrawn from the market. OFORTA was approved under the accelerated pathway on 12/18/2008 for the treatment of chronic lymphocytic leukemia. On 2/10/2011, FDA requested that the drug be voluntarily withdrawn from the market for not fulfilling the post-marketing requested that confirmed its clinical benefit. As of 12/31/2011, the drug was effectively withdrawn from the market (Johnson et al., 2011).

Discussion

The accelerated approval process was established in the year 1992 to aid in faster approval of drugs intended to treat life threatening conditions with no or limited treatment options with approval based on surrogate endpoints (FDA, 2018). Since surrogate endpoints are only predictors of clinical outcomes and not actual clinical outcomes, there are safety and efficacy concerns surrounding the early approval and introduction of drugs in the market. With the aim of further exploring the reliability of surrogate endpoints and efficacy of accelerated approval process, different aspects of the applications approved under the accelerated approval process for the time period July, 2008 - December, 2017 were reviewed. The results obtained were compared with the results of the report for the time period June, 1992- November, 2008 submitted by Government Accountability Office (United States Government Accountability Office & United States Congress. Senate Committee on Finance, 2009).

Per the GAO report, 90 applications were approved under the accelerated approval pathway within a time span of 16 years (1992-2008).An average of 5 applications per year was approved during this time. Forty-two point two percent of those applications were oncologic drugs. Other applications were primarily for HIV and inhalation anthrax. As per the analysis done in this study, 82 applications were approved just in the last 7 years (2008-2017). There is an upward yearly trend seen in the number of applications using accelerated approval. The average number of applications approved per year has increased from 5 (1992-2008) to 8.2 (2008-2017). Also, in comparison to 42.2% of oncology applications approved

during years 1992-2008, there has been a remarkable increase in the number of oncology applications approved during the years 2008-2017. The number is now up to 81.7% and looks like this pathway is becoming the lifeline for cancer patients. There are also newer indications being reviewed under this process, which means newer surrogate endpoints are being considered. This approval process has certainly provided more treatment options to seriously ill patients in the last few years.

In review of the total post-marketing studies requested for the period 1992-2008, 64 % were closed (either fulfilled or released) and 36% of studies were in open status. Per the analysis done in this report for the period 2008- 2017, 45.2% studies are closed meaning the clinical benefits were confirmed and reliance on surrogate endpoints was established, whereas 54.8% of the studies are still in open status. Even though an increasing number of applications are being approved under this pathway, the number of studies being fulfilled is less. It is not certain as to why an increase of 18.8% in open studies is seen in the last 7 years. It could suggest a few possibilities: 1) the surrogate endpoints chosen are either not successful in confirming proof of clinical benefit as expected or are taking unusually longer time; 2) sponsors could be facing other variable hindrance (like patient recruitment, complexity in design of studies etc.) in successfully fulfilling the studies which is subject to further examination; 3) many of these open studies (45.5%) are needed for the drugs approved in 2016 and 2017. They are fairly recent drugs and likely possible that they will be completed in accordance with the average time taken for the period 2008-2017.

On a positive note, more studies are now being fulfilled in less than 5 years and this percentage has increased nearly by 20.3% in comparison to the GAO report. The percentage

of studies that remained open for greater than 5 years during 1992-2008 was 29%, however, this number has come down to 23.5% for the time period 2008-2017. The average age of open studies for the time period 2008-2017 is roughly 3.21 years and majority has been open for 1-2 years. In comparison to GAO's report, there is a decrease of 6.3% seen in average age of open studies for 2008-2017. There is definitely a greater trend seen in the completion of post marketing studies and going by this, there is a good chance that a lot of the open studies may be fulfilled in the next couple of years.

Another important finding is that majority of the open studies for the period 2008-2017 are for oncology drugs. Most of these approved oncology products during 2008-2017 were either target specific antibodies or immune modulating drugs and their mechanism of action are very different from the standard chemotherapy. These drugs act by targeting certain specific receptors or molecules in the body (NIH, Biological Therapies for Cancer, 2018). The molecules that are responsible for the growth and spread of tumor are blocked which in turn inhibits the spread of cancer (NIH, Targeted Cancer Therapies, 2018). The most common surrogate endpoints used as seen in this study are progression free survival, overall survival, duration of response and tumor response rate. The studies designed to establish the effectiveness of these drugs are very complex due to different mechanism of actions and interactions involved (Fox, Curt, & Balis, 2002). An issue with these targeted drugs is also that tumors develop early resistance to them and may take longer to show clinical benefit (Sharma, Hu-lieskovan, Wargo, & Ribas, 2017). These issues are possibly responsible for the delay in completion of post marketing studies required under the accelerated approval process.

In comparison, according to the GAO report, the majority of the post-marketing studies during 1992-2008 were requested for HIV drugs and they comprised the bulk of open studies (United States. Government Accountability Office & United States Congress. Senate Committee on Finance, 2009). It was easier for the HIV confirmatory studies to be conducted because the sponsors only had to continue the study that initially led to the original approval of drug under the accelerated pathway. Sponsors did not have to design any new randomized trials. The trials conducted to obtain accelerated approval for HIV drugs were typically 24-week randomized clinical trials and to fulfill the post-marketing requirements, the sponsors had to continue the same study for another 24 weeks with the same patients and endpoints (United States. Government Accountability Office & United States Congress. Senate Committee on Finance, 2009).Thus, the increasing number of targeted oncology applications in the recent years can likely explain the reason for higher number of open studies during the period 2008-2017 as compared to 1992-2008.

Additionally, FDA did exercise its regulatory authority in withdrawing one drug from the market for lack of clinical efficacy; however, there are quite a few drugs which have been in the market for long time and are yet to prove their clinical benefits. Perhaps, if FDA clearly defines the acceptable time period within which the studies must be fulfilled barring which stringent regulatory actions like drug withdrawal would be taken might propel the sponsors to adhere to better study development plan.

Conclusion

Upon reviewing and comparing the applications and status of post-marketing studies requested under the accelerated approval process for the two time periods (1992-2008 and 2008-2017), various trends were noticed. With an increase in the number of applications being approved, there is also an increase in the number of post-marketing studies in open status. There is definitely a greater trend seen in the completion of post-marketing studies. There is a decrease of 6.3% seen in average age of open studies for 2008-2017 as compared to 1992-2008. More studies are now being fulfilled in less than 5 years. There is more number of closed studies in comparison to open studies from 2008 to 2012 and the trend slowly shifts starting 2013. Most of the post-marketing studies requested for the time period 2008-2017 are for oncology drugs. These studies can be complex to design and conduct as the drugs are target specific, hence can have longer completion timelines. This can likely explain why more number of studies is in the open status in the last 7 years. Undoubtedly, the accelerated approval pathway has provided patients with life threatening conditions faster access to promising drugs to patients, there is however still a need to closely monitor the progress of the validation trials and review the reliability of surrogate endpoints. There is also a further need to assess the hindrances being encountered by the sponsors in fulfilling these studies and come up with solutions to address them.

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Appendix A

NDAs and BLAs-Approved based on surrogate endpoints under Accelerated Approval Process

July 01, 2008 to Dec 31, 2017

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
1	Alimta (Pemetrexed disodium)	NDA021462 Supplement 021	9/26/2008	Nonsquamous Non—small cell lung cancer	Overall survival	1	Fulfilled-1
2	Promacta (Eltrombopag)	NDA022291	11/20/2008	Thrombocytopenia in patients with chronic immune(idiopathic) thrombocytopenia (ITP)	Response rate defined as an increase from baseline platelet count to a count >= 50,000/mcl	2	Fulfilled-2
3	Oforta (Fludarabine phosphate)	NDA 022273	12/18/2008	Adult patients with B cell Chronic Lymphocytic Leukemia (CLL)	Progression free survival	1	Terminated-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
4	Gleevec (Imatinib Meslylate)	NDA 021588 Supplement 25	12/19/2008	Gastrointestinal Stromal Tumors	Recurrence-free survival (RFS)	4	Fulfilled-4
5	Avastin (Bevacizumab)	BLA 125085 Supplement 169	5/5/2009	For the treatment of glioblastoma with progressive disease following prior therapy	1. Progression-free Survival (PFS) as Assessed by Investigator 2. Overall Survival (OS)	1	Fulfilled-1
6	Folotyn (Pralatrexate)	NDA22468	9/24/2009	Relapsed or refractory Peripheral T-Cell Lymphoma	Overall response rate including 1. Complete response 2.Complete response unconfirmed 3. Partial response 4. Duration of response 5. Progression free survival 6. Overall survival	2	Delayed-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
7	Arzerra (Ofatumumab)	BLA 125326	10/26/2009	For the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to Fludarabine and Alemtuzumab	1.Progression-Free Survival (PFS), as Assessed by the Independent Review Committee (IRC) 2. Number of Participants With the Best Overall Response (OR), as Assessed by the IRC	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
8	Tykerb (Lapatinib)	NDA 022059 Supplement 7	1/29/2010	Hormone receptor positive metastatic breast cancer	1.Time to progression(interval between the date of randomization and the earliest date of either disease progression or death due to breast cancer without prior progression) 2. Overall survival	2	Submitted-1 Terminated-1
9	Tasigna (Nilotinib)	NDA 022068 Supplement 5	6/17/2010	For the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase		1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
10	Sprycel (Dasatinib)	NDA 021986 Supplement 8	10/28/2010	Philadelphia chromosome positive (PH+) Chronic Myeloid Leukemia	Best Confirmed Complete Cytogenetic Response (cCCyR) Within 12 Months	1	Fulfilled-1
11	Afinitor (Everolimus)	NDA 022334 Supplement 6	10/29/2010	Subependymal giant cell astrocytom a(SEGA) associated with tuberous sclerosis (TS)	1.Progression free survival 2. Overall survival	2	Fulfilled-2
12	Makena (Hydroxyprogesterone Caproate)	NDA21945	2/3/2011	To reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.	1.Percent of births occurring at <37 weeks gestation 2. Percent of births at <35 weeks at <32 weeks gestation 3. A composite index of neonatal morbidity and mortality.	2	Delayed-1 Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
13	Istodax (Romidepsin)	NDA22393 S-4	6/16/2011	For the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.	1. Objective response rate 2. Response duration	1	Ongoing-1
14	Adcetris (Brentuximab Vedotin)	BLA125388	8/19/2011	The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.	Overall response rate	2	Fulfilled-2
15	Adcetris (Brentuximab Vedotin)	BLA 125388 Supplement 6	8/19/2011	The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.	Progression free survival	2	Fulfilled-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
16	Xalkori (Crizotinib)	NDA 202570	8/26/2011	Non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive	1. Overall survival 2. Overall Survival Probability at Months 6 and 12 3. Percentage of Participants With Objective Response (OR)	2	Fulfilled-1 Released-1
17	Ferriprox (Deferiprone)	NDA21825	10/14/2011	Treat iron overload in patients with sickle cell disease and transfusional hemosiderosis who have not been adequately treated with available chelating agents.	1.Serum ferritin levels 2. The change in Liver iron concentration after one year of treatment with deferiprone	1	Delayed-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
18	Afinitor (Everolimus)	NDA 022334 Supplement 17	4/26/2012	Adults with renal angiomylolipoma and tuberous sclerosis complex(TSC)	1.Angiomyolipoma Response Rate as Per Central Radiology Review 2. Time to Angiomyolipoma Progression as Per Central Radiology Review 3. Skin Lesion Response Rate as Per Investigator 4. Percentage of Participants With Renal Impairment	1	Fulfilled-1
19	Kyprolis (Carfilzomib)	NDA 202714	7/20/2012	Multiple Myeloma	1.Progression-free Survival (PFS)	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
20	Marqibo (Vincristine Sulfate Liposomes)	NDA202497	8/9/2012	For the treatment of adult patients with Philadelphia chromosome-negative (Ph-) acute lymphoblastic leukemia (ALL) in second or greater relapse or whose disease has progressed following two or more anti-leukemia therapies.	1. Complete remission 2.Complete remission with incomplete blood count recovery	1	Terminated-1
21	Afinitor Disperz (Everolimus)	NDA 203985	8/29/2012	Tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA)	1.SEGA response rate as determined by independent central radiology review 2. Absolute change in seizure frequency from baseline to week 24 3. Time to SEGA progression 4. Skin lesion response rate	2	Fulfilled-1 Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
22	Synribo (Omacetaxine mepesuccinate)	NDA 203585	10/26/2012	Chronic myeloid leukemia	1. Major cytogenetic response for patients with CP-CML in the CML-300 analysis 2. Major hematologic response	1	Fulfilled-1
23	Iclusig (Ponatinib)	NDA 203469	12/14/2012	Chronic myeloid leukemia	1. Major Cytogenetic Response (MCyR) 2. Major Hematologic Response	4	Fulfilled-4

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
24	Sirturo (Bedaquiline)	NDA204384	12/28/2012	For the use of SIRTURO (bedaquiline) 100 mg tablets as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB)	1.Time to sputum culture conversion 2. Analysis of relapse 3.Time to culture conversion at Week 72 4.Mortality rate	1	Ongoing-1
25	Exjade (Deferasirox)	NDA 021882 Supplement 15	1/23/2013	Thalassemia syndromes	1.Liver Iron concentration 2.Serum ferritin	3	Ongoing-3
26	Pomalyst (Pomalidomide)	NDA 204026	2/8/2013	Multiple myeloma	1. Progression free survival (PFS) defined as the time from date of randomization to the date of progression or death due to any cause, whichever occurred first.	2	Fulfilled-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
27	Elaprase (Idursulfase)	BLA 125151 Supplement 184	6/24/2013	Hunter Syndrome	1. Change in urinary glycols-aminoglycan (uGAG) levels 2. Minute walk test	2	Ongoing-1 Pending-1
28	Perjeta (Pertuzumab)	BLA125409 S-51	9/30/2013	Use of pertuzumab in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer	1. Pathological complete response	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
29	Imbruvica (Ibrutinib)	NDA205552	11/13/2013	Mantle cell lymphoma	1. Progression free survival 2. Overall response rate 3. Duration of response	2	Ongoing-2
30	Mekinist (Trametinib)	NDA 204114 Supplement 1	1/8/2014	For the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.	Progression free survival	1	Fulfilled-1
31	Tafinlar (Dabrafenib)	NDA 202806 Supplement 2	1/9/2014	In combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test	Progression free survival	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
32	Imbruvica (Ibrutinib)	NDA205552 original 2	2/12/2014	For the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy.	1. Overall response rate 2. Duration of response	2	Fulfilled-1 Released-1
33	Northera (Droxidopa)	NDA203202	2/18/2014	For the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.	Mean change in ambulatory Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 from randomization to Week 4 of the randomized withdrawal period	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
34	Zykadia (Ceritinib)	NDA 205755	4/29/2014	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.	1. Overall response rate 2. Response duration	1	Fulfilled-1
35	Beleodaq (Belinostat)	NDA206256	7/3/2014	For treatment of patients with relapsed or refractory peripheral T-cell lymphoma	1. Tumor response rate 2. Duration of response	2	Delayed-2
36	Zydelig (Idelalisib)	NDA205858	7/23/2014	For relapsed follicular B-cell non-Hodgkin lymphoma (FL) in patients who have received at least two prior systemic therapies and relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies	Overall response rate	4	Ongoing-1 Released-2 Pending-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
37	Keytruda (Pembrolizumab)	BLA 125514	9/4/2014	For the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, ifBRAF V600 mutation positive, a BRAF inhibitor.	1. Tumor response rate 2. Durability of response	1	Fulfilled-1
38	Blincyto (Blinatumomab)	NDA125557	12/3/2014	Treatment of Philadelphia chromosomenegative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	Overall survival	1	Fulfilled-1
39	Blincyto (Blinatumomab)	NDA125557: S-13	12/3/2014	B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% in adults and children	MRD response rate and hematological relapse-free survival.	2	Pending-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
40	Lynparza (Olaparib)	NDA206162	12/19/2014	Monotherapy for patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy	1. Objective response rate 2. Duration of response	2	Fulfilled-1 Released-1
41	Opdivo (Nivolumab)	BLA125554	12/22/2014	Unresectable or metastatic melanoma	1. Tumor response rate 2. Durability of response	1	Delayed-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
42	Ibrance (Palbociclib)	NDA 207103	2/3/2015	In combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.	1. Investigator-assessed Progression free survival. 2. Progression free survival based on blinded independent central review 3. Time to progression	1	Fulfilled-1
43	Farydak (Panobinostat)	NDA205353	2/23/2015	For the use of FARYDAK® (panobinostat) in combination with bortezomib (BTZ) and dexamethasone (Dex), for the treatment of patients with multiple myeloma (MM), who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.	Progression free survival	2	Delayed-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
44	Jadenu (Deferasirox)	NDA 206910	3/30/2015	For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L	Reduction of liver iron concentrations and serum ferritin levels	4	Fulfilled-1 Ongoing-3

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
45	Jadenu (Deferasirox)	NDA206910	3/30/2015	For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older and for the treatment of chronic iron overload in patients 10 years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron concentration (LIC) of at least 5 milligrams of iron per gram of liver dry weight (mg Fe/g dw) and a serum ferritin greater than 300 mcg/L.	1. Serum Ferritin 2.Liver Iron concentration	4	Fulfilled-1 Ongoing-3
46	Ferriprox (Deferiprone)	NDA208030	9/9/2015	Transfusional iron overload due to thalassemia syndromes	1.Measure changes in cardiac iron concentration 2. Liver iron concentration.	1	Delayed-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
47	Opdivo (Nivolumab)	BLA125554 S-2	9/30/2015	Unresectable or metastatic, BRAF V600 wild-type melanoma	1. Tumor response rate 2. Durability of response	1	Delayed-1
48	Keytruda (Pembrolizumab)	BLA125514 S-5	10/2/2015	For the treatment of patients with metastatic, PD-L1 positive, non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.	1. Tumor response rate 2. Durability of response	1	Fulfilled-1
49	Praxbind® (Idarucizumab)	BLA761025	10/16/2015	Indicated in patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding.	The maximum reversal of Ecarin Clotting Time or Dilute Thrombin Time in the first 4 hours was the primary endpoint	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
50	Tagrisso (Osimertinib)	NDA 208065	11/13/2015	For the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDAapproved test, who have progressed on or after EGFR TKI therapy.	1.Tumor response rate 2.Duration of response	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
51	Darzalex (Daratumumab)	BLA 761036	11/16/2015	For treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulato1y agent or are double refracto1y to a proteasome inhibitor and an immunomodulato1y agent.	Overall response rate defined as the proportion of patients who achieve a partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) based on the International Myeloma Workshop Consensus Panel 1 criteria using results from a central laboratory.	2	Fulfilled-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
52	Alecensa (Alectinib)	NDA208434	12/11/2015	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	1.Tumor response rate 2.Duration of response	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
53	Opdivo (Nivolumab)	BLA125554 S-7	1/23/2016	1)Expansion of the indication for opdivo(Nivolumab) in combination with Ipilumab for the treatment of patients with unresectable or metastatic melanoma to remove the restriction for the treatment of only patients with BRAF wild-type melanoma, 2) Expansion of the indication for Opdivo(Nivolumab) as a single agent for the treatment of patients with BRAF V600 mutation positive, unresectable or metastatic melanoma to remove the restriction that such patients should have disease progression following ipilumab and a BRAF inhibitor	Progression free survival	2	Submitted-2

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
54	ProvayBlue™ (Methylene Blue)	NDA204630	4/8/2016	For the treatment of pediatric and adult patients with acquired methemoglobinemia	Methemoglobin decrease of at least 50% at one hour after IV administration of ProvayBlue® Injection,	1	Pending-1
55	Venclexta (Venetoclax)	NDA208573	4/11/2016	For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.	1.Overall response rate	1	Fulfilled-1
56	Opdivo (Nivolumab)	BLA125554 S-19	5/17/2016	For the treatment of patients with classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.	1.Progression free survival by IRC 2.Overall survival	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
57	Tecentriq (Atezolizumab)	BLA 761034	5/18/2016	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.	Overall response rate	1	Submitted-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
58	Ocaliva (Obeticholic Acid)	NDA207999	5/27/2016	For the treatment of primary biliary cholangitis (PBC) in combination with URSODEOXYCHOLIC ACID (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA	1.Reduction in alkaline phosphatase 2.Gamma-glutamyl transferase (GGT) reduction 3.Reduction of serum transaminase (ALT and AST)	3	Ongoing-2 Pending-1
59	Keytruda (Pembrolizumab)	BLA- 125514 S-9	08/05/2016	For the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after platinum-containing chemotherapy.	1. Tumor response rate 2. Durability of response.	1	Submitted-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
60	Exondys 51 (Eteplirsen)	NDA206488	9/19/2016	For the treatment of Duchenne muscular dystrophy (DMD) in patients who have confirmed mutation of the DMD gene that is amenable to EXON 51 skipping	Increase in dystrophin	1	Pending-1
61	Lartruvo (Olaratumab)	BLA 761038	10/19/2016	In combination with doxorubicin for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline- containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery	1.RECIST 1.1 2.Progression free survival	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
62	Rubraca (Rucaparib)	NDA209115	12/19/2016	For the treatment of patients with deleterious BRCA mutation (Germline And/Or Somatic) associated advanced ovarian cancer who have been treated two or more chemotherapies.	Objective response rate	2	Fulfilled-1 Released-1
63	Imbruvica (Ibrutinib)	NDA 205552 Supplement 16	1/18/2017	For treatment of patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy	1. Overall response rate 2. Duration of response 3. .Progression free survival	1	Fulfilled-1
64	Opdivo (Nivolumab)	BLA125554 S-24	2/2/2017	High Risk Invasive Urothelial Carcinoma	1.Disease free survival (DFS 2.Non-Urothelial track recurrence free survival	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
65	Keytruda (Pembrolizumab)	BLA125514 S-15	3/14/2017	For the treatment of adult and pediatric patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy	1.Tumor response rate 2.Durability of response	1	Ongoing-1
66	Bavencio (Avelumab)	BLA761049	3/23/2017	For the treatment of adults and pediatric patients 12 years and older with metastatic merkel cell carcinoma	1.Overall response rate 2.Complete response rate 3.Partial response rate	1	Pending-1
67	Tecentriq (Atezolizumab)	BLA 761034 S-1	4/17/2017	Provides for an expansion of the indication for tecentriq (Atezolizumab) to include patients who are not eligible for cisplatin containing chemotherapy	Overall response rate	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
68	Opdivo (Nivolumab)	BLA125554 S-31	4/25/2017	For the treatment of adult patients with classical hodgkin lymphoma that has relapsed or progressed after: autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vendotin, or 3 or more lines of systemic therapy that includes autologous HSCT	Progression free survival by Independent review committee	1	Ongoing-1
69	Alunbrig™ (Brigatinib)	NDA208772	4/28/2017	For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.	1.Objective response rate as determined by clinical investigator 2. Objective response rate as determined by independent review committee	1	Pending-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
70	Imfinzi (Durvalumab)	BLA 761069	5/1/2017	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.	Objective response rate	1	Pending-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
71	Bavencio (Avelumab)	BLA 761078	5/9/2017	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy.	1.Confirmed Overall Response Rate (ORR) 2. Duration of response	1	Pending-1
72	Keytruda (Pembrolizumab)	BLA125514 S-16	5/10/2017	For the use of pembrolizumab, in combination with pemetrexed and carboplatin, for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer	1. Tumor response rate 2. Progression free survival	1	Fulfilled-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
73	Jadenu Sprinkle (Deferasirox)	NDA207968	5/18/2017	1.For the treatment of chronic iron overload in patients 10 years of age and older with nontransfusion-dependent thalassemia (NTDT)syndromes and with a liver iron concentration (LIC) of atleast 5 milligrams of iron per gram of liver dry weight (mg FE/G DW) and a serum ferritin greater than 300 mcg/l 2.For the treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older	1. Reduction in LIC (liver iron concentration) of greater than or equal to 3 mg Fe/g dry weight for baseline values greater than or equal to 10 mg Fe/g dry weight, reduction of baseline values between 7 and less than 10 to less than 7 mg Fe/g dry weight, or maintenance or reduction for baseline values less than 7 mg Fe/g dry weight.	4	Fulfilled-1 Ongoing-3

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
74	Keytruda (Pembrolizumab)	BLA125514 S-17	5/18/2017	For the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy .	1. Tumor response rate 2. Duration of response	1	Ongoing-1
75	Keytruda (Pembrolizumab)	BLA125514 S-14	5/23/2017	For the treatment of adult and pediatric patients with: 1)unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or 2)metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.	1. Tumor response rate 2. Durability of response	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
76	Opdivo (Nivolumab)	BLA125554 S-34	7/31/2017	For the treatment of adult and pediatric patients 12 years and older with microsatellite instability high (MSI-H) or mismatch repair deficient (DMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyramidine, oxaliplatin and irinotecan	1. Overall response rate 2. Duration of response	1	Ongoing-1
77	Benznidazole	NDA209570	8/29/2017	For the treatment of Chagas disease (American Trypanosomiasis), caused by Trypanosonoma Cruzi, in pediatric patients 2 to 12 years of age.	Reduction of conventional serology titers and conversion to negative of unconventional assays (immune responses to specific trypomastigote antigens F-29 and AT-ELISA	1	Pending-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
78	Aliqopa (Copanlisib Hydrochloride)	NDA209936	9/14/2017	For the treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least 2 prior systemic therapies.	1.Objective response rate 2.Progression free survival	1	Pending-1
79	Opdivo (Nivolumab)	BLA125554 S-41	9/22/2017	For the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib	1. Tumor response rate 2. Durability of response	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
80	Keytruda (Pembrolizumab)	BLA125514 S-24	9/22/2017	For the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whoe tumors express PDL-1 [(combined positive score(CPS)>=1] as determined by an FDA approved test with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- And platinum containing chemotherapy and if appropriate HER2/NEU targeted therapy	1. Objective response rate (ORR) per RECIST version 1.1. 2.Duration of response (DoR)	1	Ongoing-1

Serial #	Drug Name	NDA/BLA number	Approval Date	Approved indication	Surrogate end points	# of Post-marketing Studies Requested	Status of each study
81	Calquence (acalabrutinib)	NDA210259	10/31/2017	For the treatment of adult patients with mantle cell lymphoma(MCL) who have received at least on prior therapy.	Overall Response Rate (ORR) as defined by investigator assessed CR or PR per Lugano (2014) criteria	1	Pending-1
82	Bosulif (Bosutinib Monohydrate)	NDA203341 S-9	12/19/2017	For the treatment adult patients with newly diagnosed chronic phase (CP) Philadelphia chromosome positive chronic myelogenous leukemia (PH + CML)	1. Major Molecular Response at Month 12 2. Complete Cytogenetic Response by Month 12	1	Pending-1