Comparison in Oncological Indication Approval Policies between the United States and Europe

by

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Abstract

Pharmaceuticals are crucial in the treatment of diseases and management of other health issues and thus should be effective, safe, and timely. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) are the main regulatory bodies that oversee the development, review, and approval of pharmaceuticals, including oncologic agents for treating cancer. Even though these two bodies use similar data sets for similar pharmaceutical agents, they often arrive at different indications and approval periods and normally use different endpoints. This study retrieved public assessment reports including summaries of product characteristics and drug approval packages from respective agencies' websites. The aim of this study was to examine the differences between the two agencies by comparing review time data, exact wording used in indication, endpoints used in the reviews, and approval of 15 oncologic agents approved between 2007 and 2018. The analysis showed that on average, the FDA approved the same agent 193.15 days faster than EMA did. The study found that the FDA had shorter review periods than EMA. There were also differences in the types of endpoints used by the two agencies. The FDA used surrogate endpoints more often than the EMA. Overall survival (OS) was used as a primary endpoint by the FDA to approve approximately 27% of the agents, while EMA used overall survival as a secondary endpoint in approving approximately 60% of the agents. The differences in approvals between the FDA and EMA may reflect the differences in the regulatory processes and use of differing measures of efficacy.

Key words: Food and Drug Administration, European Medicines Agency, overall survival, oncology, professional labeling

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Introduction

Pharmaceuticals are crucial in the treatment of diseases and management of other health issues. It is important that they are effective, safe, and timely so that they can help in combating the diseases and infections they are meant for. Regulation of development and marketing of pharmaceuticals is overseen by several agencies, depending on the region. For instance, in United States, the agency tasked with regulating development and approval of pharmaceuticals is the Food and Drug Administration (FDA). Its counterpart in Europe is the European Medicines Agency (EMA). According to Pitts, Louet, Moride, and Conti (2016), these two major regulatory bodies rely on similar data sets derived from controlled trials during the review and subsequent approvals in their respective markets. Oncologic agents are one of the categories of drugs these two agencies review based on the same data set.

Oncologic agents are important products used in the fight against cancers. However, several studies (Mailankody & Prasad, 2015; Makuch & Shi, 2014; Naci, Smalley, & Kesselheim, 2017) have highlighted the complexity of similar data sets from controlled trials in coming up with correct indications and approval recommendations. These studies argue that these controlled trials require careful and thorough analyses to ensure that the right indication is approved for these oncologic agents.

Even though these two regulatory bodies use the same data set when deciding on indications, they often come up with different indications for the oncologic agents. While rapid access to new agents for patients is vital, obtaining the correct indication remains paramount in order to maximize patient benefit and minimize risk. This study assessed differences between the regulatory agencies in indications for oncologic agents approved between the years 2007 and 2018 and postulates why these differences might exist.

Background

FDA Approval Process: Pre-Approvals

According to the information obtained from the FDA (2019), pre-approval begins with the submission of Investigational New Drug application (IND) to the FDA before the investigational drug is exposed to any patient. Once the FDA receives IND, it will have up to 30 days to either put the IND on hold or to provide comments about the proposed protocol. If the FDA does not contact the sponsor after this period has expired, then it is generally assumed that the protocol may proceed. The protocol goes into Phase I and Phase II trials, which should be followed unless the agent is authorized through the expedited program.

Information obtained from the FDA (2016; 2017) suggested that at the completion of the two phases, the sponsor shall request a meeting that signifies an End of Phase 2 (EOP2) and presents the results of the trials so as to obtain an agreement for the registration path for the drug to be approved. This input is non-binding to the sponsor. The sponsor may wish to request the Special Protocol Assessment (SPA) to help in determining whether the protocol has met strict scientific and regulatory standards. With the receipt of the SPA, the FDA will be required to provide input within 45 days where they can either agree with the sponsor's assertion of the protocol or request that the sponsor make some changes to the protocol. The FDA should then go ahead and provide a written agreement known as a signed SPA, which shall be binding and may lead to approval or market authorization.

Approval/Market Authorization in the US

Approval or market authorization in the US follows when there is sufficient evidence that the FDA safety and effectiveness standards for the drug have been met. The sponsor then submits a New Drug Application (NDA) to the FDA. According to the FDA (2017), the NDA is

aimed at providing enough information to permit the FDA to assess whether the drug is safe and effective for the proposed indication, whether the proposed labeling is appropriate, and whether the manufacturing and quality control methods used can assure the quality, strength, purity, and identity of the drug.

Alternatively, as the FDA (2013) explained, the sponsor may submit to the FDA Biological Licensure Application (BLA) which is a request by the sponsor for permission to introduce a biological product into the market. These include submission of all relevant information that documents that a drug may be approved for market. These include submission of all relevant information that documents that a drug may be approved for market. During the approval of the drug, all of this information is summarized in the labeling of the product (or in SmPC in EU). This labeling is a document that provides details relevant to the new drug prescriber, including how the drug is administered, adverse effects, safety profile, target patient population, and other relevant information. The sponsor submits the NDA with all documentation found in the Common Technical Document (CTD), which includes efficacy, safety, toxicology, clinical pharmacology, chemistry manufacturing control, clinical study reports, and statistics. Also, all clinical datasets that have been prepared for analysis are submitted. After submitting the NDA, the FDA has 60 days to determine whether it is complete. On the 74th day, the FDA issues a letter that states whether the NDA is accepted for submission. If it is accepted, it is then filed, with details as to whether it will be subjected to standard or priority review.

Oncologic Agents Review

The FDA review process is very specialized. The FDA has qualified oncologists, hematologists, and other experts who are tasked with several functions, including reviewing an

NDA for oncology agents. However, there are cases where those employed by the FDA do not have the expertise required for a particular oncologic agent review. Most often, as pointed out by several studies (Garattini, 2016; Zeitoun, Lefèvre, Downing, Bergeron, & Ross, 2015; Zhang, Hueser, & Hernandez, 2017), the FDA seeks the expertise of external consultants to provide scientific advice that could assist in the evaluation of regulated agents as well as in making decisions that have a scientific basis. These independent external experts are also valuable in providing advice on the best general criteria that could be broadly used for evaluation of general medical products.

All consultants are either Special Government Employees (SGE) or federal employees who do not have any conflict of interest (FDA, 2015) in any of the projects under review. The Office of Hematology and Oncology Products (OHOP), and specifically the Division of Hematology Oncology Toxicology (DHOT), utilizes experts during the Oncology Drug Advisory Committee (ODAC) meetings as well as during the reviews of specific protocols submitted under SPA. The SPA, as noted above, provides a binding agreement between the FDA and the sponsor, with respect to the clinical study, that potentially leads to the approval of the agent. Therefore, this means that external experts' services are critical to the FDA during both IND and NDA phases of drug development. For each application, consultants are screened for conflicts as they are prohibited from participating in any official action in which they have financial interest.

The primary means through which the FDA obtains scientific advice are advisory committees (AC). This is because the ACs are presumed to be independent and therefore could not be influenced by the FDA or a sponsor. Also, ACs are presumed to be experts in their specific fields and therefore would provide expert scientific-based advice. However, ACs cannot

obligate the FDA to adopt their recommendations. Again, ACs are only mandated to address specific questions that are sent by the FDA in advance.

The FDA has three main agencies that deal with the discussion of oncologic agents/products: ODAC, the pediatric subcommittee, and the Cellular, Tissue, & Gene Therapies Advisory Committee. However, for most oncologic agents and issues, ODAC meetings are where the advisory services of consultants are prominent.

The Oncologic Drugs Advisory Committee (ODAC)

The ODAC was established under 15 U.S.C. 1451 et seq.; 21 U.S.C. 321 and Federal Advisory Committee Act. This act sets the standards under which advisory committees are formed and used. The main objective of the ODAC is to advise the commissioner or designee on how to discharge responsibilities relating to the safety and efficacy of drugs for human use, as well as any other product which falls under FDA regulatory responsibility as required. The duties of the ODAC are to "review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer and make appropriate recommendations to the commissioner of food and drugs" (FDA.gov).

ODAC Committee Members

The ODAC consists of 13 core voting members, including the chairperson. Members are selected by the FDA Commissioner or a designee from among experts with background knowledge in general oncology, biostatistics, hematologic oncology, pediatric oncology, immunology oncology, or other related professions. Members of the ODAC serve for overlapping terms of up to 4 years; non-government employee members of this committee serve on this committee as Special Government Employees.

Of the core voting members of the ODEC, one may be selected by the commissioner or designee. This member should identify with the interests of the consumers, be technically qualified, and be recommended by interested persons or consumer-oriented organizations. The committee may also include one person, designated as a non-voting member, with an industry perspective.

In instances where the expert required is not available among the voting members, the commissioner or designee may select individuals or consultants, not exceeding 10 in number, to the membership of specially constituted scientific and technical advisory committees with a temporary voting designation. These specially constituted committees could also be used to form a quorum when one is unavailable.

ODAC Meetings

When there is a tentatively scheduled ODAC meeting, the federal register will publish a notice one year in advance. The ODAC holds up to 4 meetings every year and could include some cancellations or additions as the need arises. ODAC meetings could be convened as a result of several issues. For instance, the meeting could be convened when there is an NDA or a new indication for an already approved agent; when there is reported borderline evidence concerning the efficacy of an agent; or when a new efficacy endpoint is used in clinical trials.

Additionally, ODAC meetings could be scheduled in instances where special regulatory or significant safety issues have been identified. For instance, an ODAC meeting could be called when an agent, after marketing approval, is thought to contain some harm to the general users and requires a warning to be put in the labeling.. Also, through Federal Register notice, the team informs the general public of such a meeting. This follows a briefing document that is written by the oncology staff and published on the agency website.

On the day of the meeting, the committee members listen to the presentations made by both the FDA review staff and those being made by the sponsor. These presentations are then followed by open public hearings. Also, ACs discuss the question that has been drafted by the FDA concerning study design, adequacy of data, methodology, assessment of the data, and interpretation of safety and efficacy. Following these discussions, eligible voters vote on one or more questions or issues posed. Even though recommendations made by the ODAC are not binding for the FDA, studies have shown that up to 88% (Garattini, 2016) of the agents approved by the FDA were supported for approval by the ODAC. Also, about 86% (Garattini, 2016) of the drugs that were not approved were not supported for approval by ODAC.

FDA Special Approvals

The FDA has also put in mechanisms that could be used to expedite the development and approval of certain agents that are needed for serious indications. The three approaches that the FDA has created to accelerate the development and approval of such drugs include priority review, fast track, and accelerated approval. All of these mechanisms are aimed at expediting marketing approval. However, they differ in their applications.

Fast Track. This process is used to facilitate the development and review of agents that are indicated for serious diseases and fill unmet medical needs. Such agents provide a therapy where none exists. Fast track agent designation could be requested by the sponsor at any point in drug development process, and the FDA has 60 days to provide a response. This approach calls for expedited processes of review of clinical development of such agents and more frequent communication and interactions between FDA and the sponsor be established. A drug that receives fast track designation may be eligible for a rolling review. A rolling review is where a sponsor can submit completed sections of its BLA or NDA for review by FDA rather than

waiting until that point where every section of the NDA is completed before FDA can review the entire application. Normally, NDA or BLA reviews do not begin until the sponsor has submitted the entire application. In other words, fast track designations occur before submission of NDA/BLA unlike accelerated or priority reviews which form part of the approval process.

Accelerated Approval. Accelerated approval is a process where early approval is necessitated. It is expected that the drug will provide meaningful therapeutic benefit over those products that exist in the market. In some instances, this approval is made as a result of surrogate point, which is reasonably likely to predict greater clinical benefit. There is no formal process for designating accelerated approvals. Accelerated approvals in clinical development follows restrictive process that are generated by surrogate endpoints in either Phase 2 or interim Phase 3 trials. The drugs can also be approved based on the outcome of controlled trials with hard clinical endpoints that provide evidence of clinical benefits. The review process in this approach includes the NDA or BLA data submission in one package. The review process could take up to 10 months.

Priority Review. In this method of expediting development and approval of agents, the designation is given to those drugs that are believed to offer major advances in treatment compared to the existing agents. In this approach, the FDA shortens the review goal from 10 months to 6 months. The designation could be requested by the sponsor during the NDA or BLA submission, and the FDA has 45 days to respond. It also requires that NDA and BLA data be submitted in one package.

European Medicines Agency (EMA) Approvals: The EMA Approval Process

In Europe, not all pharmaceuticals are approved by EMA. Basically, there are two ways of approvals in EU. The first method is through national authorization procedures. This is where individual EU member states authorize drugs for us in their own territories. The second authorization method is through centralized authorization procedure. This processes results into a single authorization that is valid throughout the EU. This authorization is through European Commission after review done by EMA.

EMA Centralized Approach

This is where the centralized process of drug review and approval is controlled through EMA. This is where every member state of the EU has a representation on the EMA committee for medicinal products. This committee issues a single license that is valid in all EU member states. This centralized approval is mandatory for particular classes of drugs such as those for AIDS, diabetes, oncology, autoimmune diseases among other (EMA nd-a). In this harmonized approach, the formal process of SA will take between four and five months to obtain written advice. It is, however, accompanied by substantial fees. As pointed out in several studies (Garattini, 2016; Zeitoun, Lefèvre, Downing, Bergeron, & Ross, 2015; Zhang, Hueser, & Hernandez, 2017), this may sometimes require a face-to-face meeting with the sponsors, which makes EU-wide SA necessary for potential registration of studies. However, written SA response cannot be binding for the proposed indication, as advice may change.

As compared to the US, the level of involving external consultants differs with the level in which the review is being executed. For instance, at the national level, the review could involve one consultant or a group of several. Expert advisory services for EMA are provided by scientific committees, national regulatory assessors, working party members, and experts from

scientific and academic institutions. In this regulatory agency, both internal and external experts work complementarily.

Internal assessors have both regulatory responsibilities as well as their usual clinical and scientific input. They are tasked with writing reports for assessments as well as notes that are used for guidance. External experts' committees are mainly made up of clinicians who are qualified experts in a specific given clinical field. Experts play several roles in the European Union, including scientific advice, post-authorization commitments, and advice on introduction of new indications.

CHMP - Committee for Medicinal Products for Human Use

CHMP members. The CHMP committee is made up of several members, including a chair who is elected by CHMP serving members. It also consists of one member as well as an alternate who is nominated by the 28 EU member states after holding consultation with EMA's board of management. The committee has a member from Norway and an alternate member nominated by Iceland and Norway. In the committee, there are also 5 members who are selected among the experts nominated by the agencies or member states. These members are recruited to offer additional expertise in specific scientific fields. All of the selected members serve on the CHMP committee for a renewable 3-year period (EMA, n.d-b).

Role of CHMP. CHMP is an important organ of EMA that plays a critical role in the approval of medical agents in the EU. At the EU level, CHMP is responsible for carrying out the initial assessment of authorization applications in the entire EU region. Also, CHMP is mandated to assess modifications as well as extensions of an already approved agent in the market. CHMP is tasked with reviewing the medical agents' safety recommendations made by pharmacovigilance risk assessment committees.

At the national level, CHMP is given the task of evaluating all authorized medical agents whenever they are referred to the agency in case that the agent is meant to be harmonized for the EU authorization. CHMP also provides scientific advice during the development of new medical agents, provides scientific guidelines critical for market authorization, and cooperates with other international agencies such as the FDA. CHMP assesses medical agents using scientific data to determine whether the agents meet the safety, efficacy, and quality requirements that are aimed at ensuring that the agent provides higher benefits than risks.

Scientific Advisory Group-Oncology (SAGO)

For consultation purposes, CHMP creates Scientific Advisory Groups of Oncology (SAGO) to address advisory questions raised by CHMP. SAGO is established with the aim of providing independent recommendations, specifically on scientific and technical issues related to products under evaluation by the centralized regulatory procedures. They also provide scientific recommendations to referrals from CHMP as well as any other issues that are relevant to the work of EMA.

Members of SAGO. The SAGO committee is made up of experts from specific scientific fields. The committee consists of both the core group and additional experts group. The core group consists of 12 members, with various specific clinical or technical expertise, who serve for 3 years. The core group has the role of ensuring consistency and continuity within the group. The additional expert groups are called upon in the SAGO meetings whenever there is need based on their field of expertise.

CHMP appoints consumers and patients, as well as non-European Assembly countries' representatives, to attend SAGO meetings. All members of SAGO are deemed independent members who are neither members of EMA committees or European National Competent

Authorities (NCA) staff. SAGO meetings are conducted to address questions or issues raised by CHMP. These meetings are privately conducted with only the applicant being invited. The applicant is invited to provide an explanation, or a clarification of issues raised by SAGO. SAGO then responds through consensus after deliberation of all the members present. When there is no consensus on the response to the questions prompted by CHMP, the majority's conclusion, together with the contentious position, will be noted in the SAGO response to the CHMP. SAGO's answer to the CHMP, as well as their other comments on specific medical agents, is presented in the European Public Assessment Report discussions of the specific product. This report is published on the agency website immediately following marketing authorization by the EU. CHMP, like FDA, is not obligated by the opinions or positions expressed by SAGO, even though they take the SAGO advice into account.

CHMP consults SAGO on centralized marketing authorization, scientific protocol assistance, and new indications for already approved agents, as well as any other specific issues pertaining to oncologic agents. SAGO discusses oncologic agents and bases their response on clinically relevant risk/benefit evidence in case a randomized control trial is not taking place. Also, SAGO looks at the relevance of some of the composite responses and medicinal agent inspection impacts.

Accelerated Assessments in EU

This is similar to accelerated approvals in the US. Accelerated assessment, according to EMA (2019), is where EMA could be requested to rapidly assess medical agents in the centralized procedure for those medicines that "are of major interest for public health, especially ones that are therapeutic innovations." Normally, it takes approximately 210 days to evaluate

medical agents for market authorization by CHMP. This could take even longer if the applicants are requested to supply additional information in more time is granted in such cases. Upon request, CHMP could reduce the review period to 150 days in instances where the applicant provides evidence that the medical agent is of major interest to therapeutic innovation and public health. In light of the justifications given and the proposals of the rapporteurs, the CHMP makes a decision on the request for accelerated assessment. The CHMP itself may choose to lead an accelerated assessment as and when it sees appropriate. At any moment amid the accelerated assessment, the CHMP may likewise end an accelerated assessment if never again necessary and proceed with the appraisal under standard arrangements (Shah, Roberts, and Shah, 2013).

Objectives

The main objective of this study was to compare US and EU labeling of identical drugs to determine indication differences. Specifically, this study aimed to investigate the differences in approval procedures between two regulatory bodies for a series of oncological agents approved between 2007 and 2018 and to determine how these agencies used the same data to reach possibly different indications for the drug. Also, the study examines whether differences exist that might be related to the agencies' review processes.

Methods

This study selected drugs based on the type of cancer for which they were indicated, including breast, renal, prostate, metastatic, basal, gastric, mantle, Merkel, and multiple myeloma. This was done to provide a balanced representation of data. The data were collected from two primary sources:

1. European Public Assessment Reports (EPARs) including Summary of Product Characteristics (SmPC) available at the EMA website: (http://www.ema.europa.eu/ema/)
2. The US FDA website Drugs@FDA: (http://www.fda.gov/)

Inclusion criteria included new oncologic agents approved by the two agencies between the years 2007 and 2018 and indicated for breast, renal, prostate, metastatic, basal, gastric, or multiple myeloma.

The study assessed these two databases for information found in the European public assessment reports (EPARs), Summary of Product Characteristics (SmPC), and Drug Approval Packages (DAP). These documents provided information on review decisions made leading to the approval of 15 oncologic agents. Specifically, the information about primary and secondary endpoints and the use of survival and quality of life (QoL) were assessed for these 15 oncologic agents approved by the FDA and EMA between 2007 and 2018. The study assessed whether the agency based its approval on a hard-clinical endpoint or a surrogate endpoint.

Hard clinical endpoints included in this study were those defined by Samuel and Verma (2016), and Pignatti, Jonsson, Blumenthal, and Justice (2015), which include overall survival (OS) and duration of survival (DOS). A surrogate endpoint, according to Booth and Del Paggio (2017), means a quantitative measure that could be used as a substitute for a clinical endpoint

based on scientific evidence or therapeutic, pathophysiologic, or epidemiologic evidence. The surrogate endpoints included progression-free survival (PFS) and overall response rate (ORR).

Analysis

This study compared review time data for both the FDA and EMA by subtracting submission dates from approval dates for the 15 oncologic agents reviewed. The differences in review times were then obtained for all 15 agents in both the two agencies. The review times' means were then obtained for both FDA and EMA review periods, respectively. This represented the time duration in days between the period in which the oncologic agent was presented to the agency and that time when the review was completed for approval. This difference in review time then was used to note which agency delayed approval.

Also, the study assessed the differences between the types of endpoints that were used by both the FDA and EMA in reaching the approval decision for the 15 agents. The study also analyzed the use of more than two endpoints in the approval process by the two agencies. The data were entered into a Microsoft Excel document and were presented through the use of descriptive statistics.

Results

Table 1 shows the list of oncologic agents approved (N = 15) by the FDA and EMA from 2007 and 2018. The table shows the trade name of the agent, the active ingredient, and review time in days both by the FDA and EMA as well as approved indications. The average review period for one oncologic agent by the FDA was 203 days, while for EMA it was 396 days. The average delay time between FDA and EMA approvals for the same agent was 193 days. One agent that was approved by both FDA and EMA Ixabepilone was withdrawn by EMA on March 18, 2009. Also, a drug that was approved by FDA, Lorlatinib on November 2, 2018, was still under review at the end of 2018 and therefore was not included in the analysis (Table 1).

Table 1

Drugs that Were Approved by Both the FDA and EMA

Year	Trade Name	Active Ingredients	FDA Submission Date	FDA Approval Date	Total Review Period (in Days)	EMA Submission Date	EMA Approval Date	EMA Review Duration (in Days) (Submission to Approvals)	Approved Indication
2007	Ixempra	Ixabepilone	April 16, 2007	October 16, 2007	183	February 21, 2008	May 29, 2009	463	Breast cancer
2008	Alimta	Pemetrexed	May 5, 2008	September 26, 2008	164	February 23, 2008	April 23, 2009	425	NSCLC
2009	Avastin	Bevacizumab	April 20, 2009	July 31, 2009	102	April 16, 2008	May 26, 2009	405	Renal cell carcinoma
2009	Afinitor	Everolimus	June 27, 2008	March 30, 2009	276	July 23, 2008	September 2, 2009	406	Renal cell carcinoma
2010	Jevtana	Cabazitaxel	March 31, 2010	June 17, 2010	78	February 23, 2010	January 20, 2011	331	Prostate cancer
2011	Yervoy	Ipilimumab (BLA)	June 25, 2010	March 25, 2011	273	May 17, 2010	July 25, 2011	434	Metastatic melanoma
2012	Erivedge	Vismodegib	September 8, 2011	January 30, 2012	144	September 9, 2012	July 30, 2013	324	Basal cell carcinoma

Year	Trade Name	Active Ingredients	FDA Submission Date	FDA Approval Date	Total Review Period (in Days)	EMA Submission Date	EMA Approval Date	EMA Review Duration (in Days) (Submission to Approvals)	Approved Indication
2013	Imbruvica	Ibrutinib	June 28, 2013	February 12, 2014	229	February 17, 2014	October 21, 2014	246	Mantle cell lymphoma
2013	Revlimid	Lenalidomide (sNDA)	December 5, 2012	June 5, 2013	182	October 14, 2014	January 28, 2016	471	Mantle cell lymphoma
2014	Cyramza	Ramucirumab (BLA)	August 23, 2013	April 21, 2014	241	November 10, 2015	November 9, 2016	365	Gastric cancer
2015	Ninlaro	Ixazomib	July 10, 2015	March 10, 2016	244	September 19, 2015	November 21, 2016	429	Multiple Myeloma
2015	Darzalex	Daratumumab	July 9, 2015	March 9, 2016	244	April 20, 2015	May 20, 2016	396	Multiple Myeloma
2016	Lartruvo	Olaratumab	February 24, 2016	October 24, 2016	243	September 5, 2015	November 9, 2016	431	Soft tissue sarcoma
2017	Bavencio	Avelumab	September 23, 2016	May 23, 2017	242	July 22, 2016	September 18, 2017	423	Merkel cell carcinoma
2018	Lorbrena	Lorlatinib			November 2, 2018			Still under review since September 2018 (No data)	ALK+ NSCLC
Mean FDA days = 203.21 days Mean EMA days = 396.36 days Mean Delay in days (EMA - FDA) : 396.36 – 203.21 = 193.15 days									

The results show that 5 out of 15 agents analyzed (33%) were approved by the FDA through an accelerated approval mechanism, while EMA seemed to have approved all the drugs through standard approval procedures (Table 2).

Table 2

Indication Differences for Approved Oncology Agents in the United States and Europe

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Ixabepilone	To treat breast cancer that is locally advanced or metastatic in combination with capecitabine when previous treatment with cytotoxic medicines had failed.	"in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated." "As monotherapy is indicated for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracycline, a taxane, and capecitabine."	FDA approved based endpoint of progression-free survival (PFS) from the results of RCT and single arms trials. EMA withdrew based on FS, ORR, and OS	FDA-Standard Approval EMA: Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Pemetrexed	-In combination with cisplatin is indicated for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma -In combination with cisplatin is indicated for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology -Is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy -Is indicated as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology	"as a single-agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy."	FDA approved based on OS. EMA approved based on OS Hazard ratio (HR) and PFS	FDA-Standard Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Bevacizumab	Treatment of non-rhabdomyosarcoma soft tissue sarcoma. Treatment of rhabdomyosarcoma	"In combination with intravenous 5-fluorouracil–based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum." "For use in combination with carboplatin and paclitaxel, followed by Avastin as a single agent, for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection."	FDA approved based on PFS EMA approved based on Duration of Survival (DOS)	FDA-Standard Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Everolimus	-Treatment of hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. -Treatment of unresectable or metastatic, well-or moderately-differentiated neuroendocrine tumors of pancreatic origin in adults with progressive disease -Treatment of unresectable or metastatic, well-differentiated(Grade1 or Grade2)non-functional neuroendocrine tumors of gastrointestinal or lung origin in adults with progressive disease	"For the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib."	FDA approved based on a trial demonstrating a clinically and statistically significant improvement in PFS with an acceptable benefit/risk ratio. EMA approved based on PFS evaluated by Response Evaluation Criteria in Solid Tumors (RECIST).	FDA-Standard Approval EMA-Standard Approval
Cabazitaxel	In combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.	"In combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen."	Approved by FDA through PFS EMA approved based on OS	FDA-Standard Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Ipilimumab	Treatment of all conditions included in the category of malignant neoplasms (except melanoma, nervous system, hematopoietic and lymphoid tissue)	"Indicated for the treatment of unresectable or metastatic melanoma."	FDA approved based on PFS EMA approved based on improved PFS	FDA-Standard Approval EMA-Standard Approval
Vismodegib	Treatment of adult patients with: - symptomatic metastatic basal cell carcinoma - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy	"Treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation."	FDA approved based on FPS and enclosed agreed-upon labeling text EMA approved based on ORR	FDA-Standard Approval EMA-Standard Approval
Ibrutinib	Treating adult patients with the following blood cancers: -chronic lymphocytic leukemia (CLL)in previously untreated patients and in patients who have received at least one previous treatment; -mantle cell lymphoma in patients whose disease does not respond to or has come back after previous treatment; -Waldenström's macroglobulinemia (also known as lymphoplasmacytic lymphoma) in patients who have had previous treatment or who cannot have chemoimmunotherapy.	"For the treatment of patients with Mantle Cell lymphoma (MCL). -For the treatment of patients with Chronic Lymphocytic Leukemia (CLL) who have received at least one prior therapy."	FDA approved based on overall response rate (ORR) with single-arm trials and labeling EMA approved based on ORR, complete response (CR), partial response (PR) and duration of response (DOR)	FDA-Accelerated Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Lenalidomide	Treatment of mantle cell lymphoma	"Indicated for the treatment of patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5 q cytogenetic abnormality with or without additional cytogenetic abnormalities."	FDA approved based on ORR of clinical benefits of RBC transfusion independence EMA approved and withdrawn based on benefit/risk analysis	FDA-Accelerated Approval EMA-Standard Approval
Ramucirumab	To treat adult patients with: -advanced gastric cancer - metastatic colorectal cancer - non-small cell lung cancer that is advanced or has spread to other parts of the body	Indicated for advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single-agent after prior fluoropyrimidine- or platinum-containing chemotherapy.	FDA approved based on PFS, 12-week PFS, ORR, and duration of response EMA used Overall survival (OS) to approve.	FDA-Standard Approval EMA-Standard Approval
Ixazomib	Ninlaro in combination with lenalidomide and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."	"In combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy."	FDA approved based on the improvement of PFS between 4 and six months. EMA approved based on PFS	FDA-Standard Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Daratumumab	-In combination with the medicines bortezomib, melphalan, and prednisone in patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant -On its own when the disease has come back after treatment with cancer medicines and immunomodulatory medicines -In combination with dexamethasone plus either lenalidomide or bortezomib in patients who have previously received other treatment for the disease.	"For the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulato1y agent or are double refracto1y to a proteasome inhibitor and an immunome odulato1y agent."	FDA approved based on ORR, calculated as the proportion of subjects who achieved PR or better during treatment or the follow-up phase EMA approved based on PFS	FDA- Accelerated Approval EMA- Standard Approval
Olaratumab	"In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin."	"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."	FDA accelerated approval based on PFS and OS EMA approved based on PFS and secondarily on ORR and OS	FDA- Standard Approval EMA-Standard Approval
Avelumab	"Is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC)"	"For the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma."	FDA approved based on ORR and Duration of response (DOR) -EMA approved based on ORR, best overall response (BOR) and PFS.	FDA- Accelerated Approval EMA-Standard Approval

Active Ingredients	EMA	FDA Indication	Primary and Secondary Endpoints used by FDA & EMA	Regulatory Action
Lorlatinib	The treatment of patients with anaplastic lymphoma kinase-positive advanced non-small cell lung cancer.	"For the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on: •Crizotinib and at least one other ALK inhibitor for metastatic disease; or •Alectinib as the first ALK inhibitor therapy for metastatic disease; or •Ceritinib as the first ALK inhibitor therapy for metastatic disease"	FDA accelerated approval based on tumor response rate and durability of response -Under evaluation following application September 2018	FDA-Accelerated Approval EMA-No Data

Also, the FDA and EMA granted different indications for similar agents. For instance, the wording used by EMA for pemetrexed indication is "in combination…" The FDA, however, stated use "as a single agent…" for pemetrexed indication. This means that pemetrexed is used as a monotherapy drug by the FDA, while the same drug was indicated as a combination therapy by EMA (See Table 2). Bevacizumab was indicated by the FDA as a combination therapy, while EMA indicated it as a monotherapy. Both FDA and EMA indicated cabazitaxel, olaratumab, and ixazomib as combination therapy. Daratumumab is indicated as a combination of therapy by EMA (Table 2).

Also, some drugs are presented with more than one indication by one agency, while in another agency are presented with only a single indication. For instance, EMA has presented pemetrexed, everolimus, vismodegib, ramucirumumab, and daratumumab for more than one

indication, while the same drugs have been presented for only one indication by the FDA (refer to Table 2). Both the FDA and EMA presented ibrutinib for one indication. The FDA based most of its oncologic agents' reviews on surrogate endpoints, while EMA used hard endpoints to review its oncologic agents. EMA, on the other hand, used hard endpoint (OS) as a primary endpoint to approve more than 4 out of 15 (27%) agents including pemetrexed, cabazitaxel, ramucirumab, and bevacizumab. The FDA has used surrogate endpoints to approve 14 out of 15 (93%) agents, whereas EMA used surrogate to approve only 9 out of 15 (60%) of agents (Table 2).

Discussion

There is a great discrepancy between the review periods, with the long delay being seen on the part of EMA. This finding is in line with the arguments made by Alqahtani, Seoane-Vazquez, Rodriguez-Monguio, and Eguale (2015), which posited that the FDA approves oncologic agents sooner than EMA does. Another study by Downing and colleagues (2017) also pointed out that EMA takes a longer period to reach approval decisions than the FDA. This longer review period could be a result of different procedures followed during the review process. These results show that there may be different organizational policies or objectives between the FDA and EMA that account for the differences in review periods for similar drugs. For instance, the FDA has a policy of expediting most of the cancer drugs, compared to EMA, which, even though it sometimes uses accelerated review to approve some drugs, restricts approval based on the available data.

The results show that even though both agencies use similar data sets, one could ultimately reach a decision different from the other. For instance, the results show that one agent, ixabepilone, was approved by both agencies; later it was withdrawn by EMA but still remains in the U.S. market, as it has not been withdrawn by the FDA. This indicates that both the FDA and EMA have different policies and procedures that guide approvals as well as withdrawals.

The results also show that the FDA approves more oncologic agents through accelerated approval than EMA for the drugs assessed. This could be one of the reasons why EMA takes a longer time to release new agents into the market. This also indicates that EMA might have more restrictions that control which drugs will be approved through an accelerated review.

Moreover, the findings of this study show that the two agencies word the indications of similar agents differently. This may be explained by the review process that EMA follows, which

is more complex than the simpler procedures used by the FDA. EMA restricts the use of preliminary evidence and non-confirmation when reviewing the agents. While one agency approved a drug as a monotherapy, another agency approved it for combination therapy.

Additionally, the two agencies differed in the way they approved similar agents for different indications by applying different endpoints. As the two agencies generally approved these agents within a year of each other, which means that the data set they used is the same, they used different endpoints. The FDA used hard endpoints while EMA used surrogate endpoints. For instance, EMA has presented pemetrexed, everolimus, vismodegib, ramucirumumab, and daratumumab for more than one indication, while the FDA has presented the same drugs for only one indication. Even though previous studies have used different drugs and sample sizes and hence have no direct relation, these finding are generally supported by studies conducted by Kapczynski (2015) and Light and Lexchin (2015), which pointed out that the FDA and EMA could add an indication after the market authorization as long as there is additional data on the agent. This implies that even though they use similar data sets, their analyses may differ based on specific factors or subsequent information, such as additional endpoints.

A study by Pease and colleagues (2015) pointed out that the FDA used hard endpoints as its primary means of approving agents while the majority of its approvals were based on surrogate endpoints. Specifically, PFS was the endpoint most commonly used by the FDA in approving the agents under investigation. Even though OS is the most convincing endpoint in approving these agents, the FDA used it less than EMA did. This is contrary to the studies conducted by Grössmann (2017), Kim and Prasad (2015), and Nagai and Ozawa (2016), which determined that the FDA used QoL more in approval decisions. However, Jarosławski, Auquier,

Borissov, Dussart, and Toumi (2018) agreed in part with the current study that the FDA relies much on surrogate endpoints for its approval decision, as QoL is a surrogate endpoint. This implies that the FDA and EMA use the same data sets for different approvals.

According to studies conducted by Shah, Roberts, and Shah (2013) and Senderowicz and Pfaff (2014), the FDA, in particular, has approved most of these oncological drugs through accelerated approval that did not look at the patient-related benefits alone but also considered efficacy and safety. Several studies (Samuel & Verma, 2016; Pignatti, Jonsson, Blumenthal, & Justice, 2015), before the year 2012, found that most of the drugs approved by both agencies mainly looked at safety and efficacy evidence as bases for approval. This was also noted by the study conducted by Darrow and Kesselheim (2014), which argued that safety and efficacy are key determinants during review and subsequent approval decision-making.

All of these findings have several implications to medical field. To begin with, the differences in review and approvals between the two main global agencies mean that the drugs will reach markets at different times. Tafuri and colleagues (2014), Shields (2016), and Sifuentes & Giuffrida (2015) pointed out in their studies that differences in the reviews and approvals could impact not only the prescriptions but also the health of cancer patients who have to wait longer for safe and effective drugs. Given the high cost of cancer drugs, a slow market entry of new agents could mean that the cost of treating and managing cancer will increase. Several studies (Kim & Prasad, 2016; Ladanie, Ewald, Kasenda, & Hemkens, 2018; Ledanie, 2018; Liberti et al., 2015) argued that this will increase the burden of disease on cancer patients and therefore should be reviewed.

However, according to Davies and colleagues (2017), the slow approval in Europe by EMA follows a lengthy review process that has to include several experts. Also, the requirement

that all agents from the 28 member states should be involved causes the process to slow. The FDA uses several pathways in accelerating approvals, as opposed to EMA. However, EMA has also embraced accelerated assessment that could reduce the amount of time that it takes to approve the drug.

Another implication of the differences is that the use of different endpoints could negatively influence future regulatory and evaluator decisions. The increasing use of surrogates and a mix of surrogates and hard endpoints could lead to erroneous approvals that could result in a higher cost, rather than benefit, to the patients. According to Darrow and Kesselheim (2014), there are some "nonaccepted" surrogates that could lead to erroneous approval decisions.

According to Downing, Zhang, and Ross (2017) and Aronson (2017), the use of different endpoints with the same data sets by these two agents reflects that the agencies may have different policy frameworks, may experience market pressure, or may have different organizational objectives. First, a review agency such as the FDA could require a different set of standards to be met by the sponsors by following a particular specific procedure. This could lead to faster reviews or to extended reviews, based on the type of agents in question.

Second, the sponsors could influence differences in approval indication. In certain cases, sponsors have been able to tailor their products to meet specifications of a particular geographical market and hence attract faster approval than products under general review. There are high stakes and divided interests in the multi-billion cancer drug market. An agency where the market interest is strong, such as in the US, will more likely be willing to expedite the review and the approval processes. Also, the goals that the FDA pursues could be totally different from the goal of EMA. For instance, the FDA has been in the forefront of "bringing safe, effective, innovative drugs to market more quickly" (FDA, 2019). EMA, on the other hand, has been

known to provide a chance for all member states to have a say in the approval process. This not only results in a delay but also complicates the analysis and interpretation of scientific data that could result in the approval of different indications from those of the FDA.

This study had two limitations. The first weakness was the sample size used. The study used 15 oncologic agents approved between the year 2007 and 2018. This small sample size could affect the generalizability of these findings as they could not be said to be representative of the oncologic agent population. Also, the use of so few oncologic agents in each year could not be a good representation. Due to the identified limitations, future similar studies should focus on a larger sample so as to allow for generalization of the findings. Also, future studies should look at other, less complex agents to ensure that the differences observed here were a result of the complex nature of the oncologic agents' data.

Conclusion

This study assessed the resultant indications of oncologic drugs reviewed by both agencies, the FDA and EMA, between the years 2007 and 2018, in order to examine whether the differences that exist might be related to the agencies' review processes. The results revealed differences in the approval time, indications, use of endpoints, and regulatory actions. Also, differences in reviews between the two agencies could result in different prescriptions that could negatively impact on future reviews. These differences between the FDA and EMA suggest that the two agencies differ in their review processes, possibly as a result of different approval standards, different market pressures, or a difference in objectives between the two agencies or regions. These differences could result from the fact that FDA is a federal body while EMA is an agency of EU with many different member states therefore, their processes could differ from the point of faster decision-making process.

References

Alqahtani, S., Seoane-Vazquez, E., Rodriguez-Monguio, R., & Eguale, T. (2015). Priority review drugs approved by the FDA and the EMA: Time for international regulatory harmonization of pharmaceuticals? *Pharmacoepidemiol Drug Saf, 24*(7), 709–715.

Aronson, J. K. (2017). Post-marketing drug withdrawals: Pharmacovigilance success, regulatory problems. *Therapie, 72*(5), 555–561.

Booth, C. M., & Del Paggio, J. C. (2017). Approvals in 2016: Questioning the clinical benefit of anticancer therapies. *Nat Rev Clin Oncol*., *14*, 135–136. doi: 10.1038/nrclinonc.2017.18.

Darrow, J. J., & Kesselheim, A. S. (2014). Drug development and FDA approval, 1938–2013. *N Engl J Med*., *370*, 39. doi: 10.1056/NEJMp1402114

Davis, C., Naci, H., Gurpinar, E., Poplavska, E., Pinto, A., & Aggarwal, A. (2017). Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: Retrospective cohort study of drug approvals 2009–13. *BMJ*. *359*, 4530. doi: doi: 10.1136/bmj.j4530

Downing, N. S., Shah, N. D., Aminawung, J. A., Pease, A. M., Zeitoun, J. D., Krumholz, H. M., & Ross, J. S. (2017). Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. *JAMA, 317*(18), 1854–1863.

Downing, N. S., Zhang, A. D., & Ross, J. S. (2017). Regulatory review of new therapeutic agents—FDA versus EMA, 2011–2015. *N Engl J Med*, *376*(14), 1386–1387.

European Medicines Agency (EMA). (2005*). Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products*. Retrieved April 21, 2019, from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003637.pdf.

European Medicines Agency (EMA). (n.d-a). *The centralized procedure at EMA*. Retrieved April 20, 2019, from https://www.ema.europa.eu/en/documents/presentation/presentation-centralised-procedure-european-medicines-agency_en.pdf.

European Medicines Agency (EMA). (n.d-b). *How are medicines evaluated at the EMA –Part I*. Retrieved April 20, 2019, from https://www.ema.europa.eu/en/documents/presentation/presentation-how-are-medicines-evaluated-european-medicines-agency-part-1_en.pdf.

FDA. (2019). *FDA organization*. Retrieved April 13, 2019, from www.FDA.org.

Garattini, S. (2016). The European medicines agency is still too close to industry. *BMJ*, 353. Doi:i2412.10.1136/bmj.i2412

Grössmann, N. (2017). Wild C. Between January 2009 and April 2016, 134 novel anticancer therapies were approved: What is the level of knowledge concerning the clinical benefit at the time of approval? *ESMO Open*. *1*(6), e000125. doi:10.1136/esmoopen-2016-000125.

Jarosławski, S., Auquier, P., Borissov, B., Dussart, C., & Toumi, M. (2018). Patient-reported outcome claims in European and United States orphan drug approvals. *J Mark Access Health Policy*, *6*(1), 1542920. doi:10.1080/20016689.2018.1542920.

Kapczynski, A. (2015). The trans-pacific partnership—is it bad for your health? *N Engl J Med.*, 373, 201–3.

Kim, C., & Prasad, V. (2015). Cancer drugs approved on the basis of a surrogate end point and subsequent overall survival: An analysis of 5 years of US Food and Drug Administration approvals. *JAMA Intern Med*., 175, 1992–1994. doi:10.1001/jamainternmed.2015.5868.

Kim, C., & Prasad, V. (2016). Strength of validation for surrogate end points used in the US Food and Drug Administration's approval of oncology drugs. *Mayo Clin Proc*., pii: S0025-6196(16)00125–7.

Ladanie, A., Ewald, H., Kasenda, B., & Hemkens, L. G. (2018). How to use FDA drug approval documents for evidence syntheses. *BMJ*, 362, k2815. doi:10.1136/bmj.k2815

Ladanie, A., Speich, B., Naudet, F., Agarwal, A., Pereira, T. V., Sclafani, F., … Hemkens, L. G. (2018). The Comparative Effectiveness of Innovative Treatments for Cancer (CEIT-Cancer) project: Rationale and design of the database and the collection of evidence available at approval of novel drugs. *Trials*, *19*(1), 505. doi:10.1186/s13063-018-2877-z

Liberti, L., Stolk, P., McAuslane, J. N., Schellens, J., Breckenridge, A. M., Leufkens, H. (2015). Observations on three end point properties and their relationship to regulatory outcomes of European oncology marketing applications. *Oncologist*, *20*(6), 683–91. doi: 10.1634/theoncologist.2014-0297.

Light, D. W., & Lexchin, J. (2015). Why do cancer drugs get such an easy ride? *BMJ*; 350, h2068.

Mailankody, S., & Prasad, V. (2015). Five years of cancer drug approvals: Innovation, efficacy, and costs. *JAMA Oncol*., 1, 539. Doi:40.10.1001/jamaoncol.2015.0373

Makuch, R. W., & Shi, R. (2014). Comparison of drug approvals in Europe versus the United States: An analysis of discrepancies between drug products reviewed by EMA and FDA. *Ther Innov Regul Sci.*, *48*(3), 362–366.

Naci, H., Smalley, K. R., & Kesselheim, A. S. (2017). Characteristics of preapproval and postapproval studies for drugs granted accelerated approval by the US Food and Drug Administration. *JAMA*, *318*, 626–636. doi:10.1001/jama.2017.9415

Nagai, S., & Ozawa, K. (2016). Regulatory approval pathways for anticancer drugs in Japan, the EU and the US. *Int J Hematol*, *104*(1), 73–84.

Pease, A. M., Krumholz, H. M., Downing, N. S., Aminawung, J. A., Shah, N. D., & Ross, J. S. (2017). Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: Systematic review. *BMJ*, 357, j1680. doi: 10.1136/bmj.j1680

Pignatti, F., Jonsson, B., Blumenthal, G., & Justice, R. (2015). Assessment of benefits and risks in development of targeted therapies for cancer--The view of regulatory authorities. *Mol Oncol.*, *9*(5), 1034-41. doi:10.1016/j.molonc.2014.10.003.

Pitts, P. J., Louet, H. L., Moride, Y., & Conti, R. M. (2016). 21st century pharmacovigilance: Efforts, roles, and responsibilities. *Lancet Oncol.*, *17*(11), 486–492.

Samuel, N., & Verma, S. (2016). Cross-comparison of cancer drug approvals at three international regulatory agencies. *Current Oncology (Toronto, Ont.)*, *23*(5), e454–e460. doi:10.3747/co.23.2803

Senderowicz, A. M., & Pfaff, O. (2014). Similarities and differences in the oncology drug approval process between FDA and European Union with emphasis on in vitro companion diagnostics. *Clin Cancer Res.*, *20*(6), 1445–1452.

Shah, R. R., Roberts, S. A., & Shah, D. R. (2013). A fresh perspective on comparing the FDA and the CHMP/EMA: Approval of antineoplastic tyrosine kinase inhibitors. *British Journal of Clinical Pharmacology*, *76*(3), 396–411. doi:10.1111/bcp.12085

Shields, A. L., Hao, Y., Krohe, M., Yaworsky, A., Mazar, I., Foley, C., Mehmed, F., Globe, D. (2016). Patient-reported outcomes in oncology drug labeling in the United States: A framework for navigating early challenges. *Am Health Drug Benefits*, *9*(4), 188–97.

Sifuentes, M. M., & Giuffrida, A. (2015). Drug review differences across the United States and the European Union. *Pharmaceut Reg Affairs* 4, e156. doi:10.4172/2167-7689.1000e156

Tafuri, G., Stolk, P., Trotta, F., Putzeist, M., Leufkens, H. G., Laing, R. O., & de Allegri, M. (2014). How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers' views. *Ann Oncol.*, *25*(1), 265–269.

US Food and Drug Administration (2013). *EMA-EU MSs-FDA initiative on inspections for generic applications*. Retrieved from April 25, 2019, https://www.fda.gov/downloads/InternationalPrograms/Partnerships/UCM389459.pdf

US Food and Drug Administration (EMA). (2015). *FDA, European Commission and EMA reinforce collaboration to advance medicine development and evaluation*. Retrieved from April 28, 2019, https://www.fda.gov/downloads/InternationalPrograms/Partnerships/UCM454589.pdf

US Food and Drug Administration (FDA). (2016). 2006–2015 Hematology/Oncology (Cancer) Approvals & Safety Notifications. Retrieved from April 28, 2019, http://wayback.archive it.org/7993/20170111064250/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

US Food and Drug Administration (FDA). (2017). Hematology/Oncology (Cancer) Approvals & Safety Notifications. Retrieved from April 27, 2019, https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Zeitoun, J. D., Lefèvre, J. H., Downing, N. S., Bergeron, H., & Ross, J. S. (2015). Regulatory review time and post-market safety events for novel medicines approved by the EMA between 2001 and 2010: A cross-sectional study. *Br J Clin Pharmacol*, *80*(4), 716–726.

Zhang, Y., Hueser, H. C., & Hernandez, I. (2017). Comparing the approval and coverage decisions of new oncology drugs in the United States and other selected countries. *J Manag Care Spec Pharm.*, *23*(2), 247–254.

Glossary

ALK+ NSCLC : Anaplastic Lymphoma Kinase-positive Metastatic Non-Small Cell Lung Cancer

BLA : Biological Licensure Application

CLL : Chronic Lymphocytic Leukemia

CHMP : Committee for Medicinal Products for Human Use

CTD : Common Technical Document

EMA : European Medicines Agency

EPAR : European Public Assessment Reports

FDA : Food and Drugs Agency

IND : Investigational New Drug

NDA : New Drug Application

ODAC : Oncology Drug Advisory Committee

ORR : Overall Response Rate

OS : Overall Survival

PFS : Progression-Free Survival

SmPC : Summary of Product Characteristics