Abstract

Drug approval ([U.S. Food and Drug Administration (FDA), or market authorization for the European Union’s European Medicines Agency (EMA)]) is the most significant regulatory milestone for any drug, as drugs can only be marketed after marketing approval by a health authority. This article focuses on the main regulatory aspects of the drug approval process in the European Union (EU) and the United States. Although the procedures, requirements, and timelines for drug approvals are different between the EU and the United States, several global harmonization efforts have been developed during the past few years to have more consistent regulatory procedures/outcomes in different parts of the world. One of the most different procedures/requirements among these regions is co-development, also known as in vitro companion diagnostic. In the United States, it is expected that for a drug that requires an in vitro diagnostic test to select the population to be treated, the companion diagnostic should be already/concomitantly approved by the FDA. In the EU, these requirements are not as stringent as in the United States. However, it is anticipated that in the very near future, legislation changes in the EU will lead to similar requirements for the companion diagnostics for EMA. In summary, although the principles, procedures, and requirements for drug approvals may differ between the United States and EMA, novel efforts to harmonize them are being considered and implemented, thereby leading to simpler global drug development. It is of outmost importance that drug developers understand and appreciate differences in regional regulations. Otherwise, lack of understanding may lead to rejection or delays in drug approvals for useful anticancer agents.

Introduction

One of the most important steps in drug development is the marketing approval of a new agent. Once approved, the agent can be prescribed to patients following the labeled indication. Traditionally, oncologic drugs were prescribed on the basis of histology/stage/line of therapy. More recently, with the molecular understanding on cancer progression, drugs are being prescribed on the basis of subgroups determined by in vitro diagnostic devices (IVD), known as co-development or companion diagnostics. In principle, enrichment strategies based on predictive IVD biomarkers would lead to smaller, quicker, and potentially less expensive clinical trials, minimizing the exposure of patients to ineffective therapies. Thus, it is crucial that sponsors, with the use of the IVD, identify the subpopulation that will benefit the most with the new investigational agent.

In this review, we attempt to provide a brief overview and comparison of the oncology drug approval process in the United States and the European Union (EU). To illustrate similarities and differences between regions, we discuss three interesting submissions with distinct outcomes in the United States and the EU. Moreover, we describe the main differences in the approval process for drugs that require an IVD. This review focuses on the approval requirements for late oncology development. Early-stage development of oncology drugs has been previously addressed elsewhere (1, 2).

Preapproval/Marketing Interactions with Regulatory Agencies (see Table 1)

United States

Before a patient is exposed to an investigational agent, the sponsor must submit an investigational new drug (IND) to
the U.S. Food and Drug Administration (FDA; ref. 1). Once the IND is received, the FDA has 30 days to provide comments to the proposed protocol or to place the IND on hold. If the FDA does not contact the sponsor, it is assumed that the protocol may proceed (1).

In general, after the completion of phase I and II trials (unless the agent is under an expedited program, see below), sponsors request an end of phase II (EOP2) meeting to present the results of the development program and to obtain agreement for the registration path for drug approval (3). EOP2 input is considered nonbinding (3). To determine whether a protocol meets strict scientific and regulatory standards to support the approval of a drug, a sponsor may request a Special Protocol Assessment (SPA; ref. 4). Once the SPA is received, the FDA is committed to providing input within 45 days. The FDA may agree with the sponsor or request that changes be made to the protocol. A written agreement, also known as a “signed SPA,” is considered binding (4).

In the EU, to start a clinical trial with an investigational agent, sponsors need to submit a clinical trial application (CTA), which is comparable with the IND in the United States. CTAs are required in each country where trials are conducted. The CTA includes the clinical protocol, investigator’s brochure, and the investigational medicinal product dossier (IMPD). The IMPD includes summaries of information related to the quality, manufacture, and control of the IMP, and data from nonclinical and clinical studies (5, 6) and requires that (i) the sponsor has a legal representative in the EU, (ii) a CTA “written approval” for each participating country, and (iii) the competent authorities register clinical trials in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database (7). It is expected that the time for approval for each country will vary.

Recently, a new procedure to improve consistency among different EU countries was adopted, voluntary harmonization procedure (VHP). The VHP for CTAs allows for a more central and homogeneous review process among the different EU countries as well as a better distribution of duties between the competent authorities. Moreover, it has standardized the content, format or language requirements, timelines for the review of an application, submission dates, etc. (8).

In the EU, the sponsor may obtain scientific advice (SA) via two different paths: either nationally (per country) or EU-wide via the Committee for Medicinal Products for Human Use (CHMP). SA can be requested at any point during the development of an IMP. There are several advantages to the national SA: the time required to obtain a face-to-face interaction is shorter (~2 months), and information obtained in the national SA may be useful for the EU-wide preparation. Of note, fees are minimal or are not required. Unfortunately, the national advice is not legally binding and it does not address ethical questions about whether a trial is acceptable in terms of patients’ rights and safety. Moreover, different countries may give different advice.

In contrast, the European SA (see Fig. 1) is a harmonized advice, a more formal process that is accompanied by

![Figure 1. Schematic representation for timelines and procedures from first in-human trials to postapproval drug development in the United States and the EU. This figure represents the potential interactions with U.S. FDA and EU EMA for the development of drugs/biologic products. Some interactions, such as EOP2, SPAs, and SAs, are not required but are recommended to have a better/more aligned global drug development.](https://example.com/figure1)

### Table 1. Interactions with health authorities (FDA/EMA) preapproval/marketing stage

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<thead>
<tr>
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<th>FDA</th>
<th>EMA</th>
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<tr>
<td>Pre-IND</td>
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<td>No</td>
</tr>
<tr>
<td>IND</td>
<td>Yes</td>
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<tr>
<td>CTA</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>EOP1/EOP2</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SA</td>
<td>Noa</td>
<td>Yesb</td>
</tr>
<tr>
<td>SPA</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SAG</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Advisory committee</td>
<td>Yes</td>
<td>Yesc</td>
</tr>
</tbody>
</table>

Abbreviations: EMA, European Medicines Agency; SAG, scientific advisory group.

aSimilar to EOP1/EOP2.
bEither nationally or centralized for the EU.
cNot public.
by substantial fees. Approximately 4 to 5 months elapse before a sponsor receives the formal written advice. A face-to-face meeting may occur as well. An EU-wide SA always should be considered before potential registration studies. However, an SA-written response is not binding and advice may change with evolution in the state of the art for the proposed indication.

Approval/Marketing Authorization Filings

United States

When the sponsor of a new drug/biologic believes that enough evidence on the drug’s safety and effectiveness has been obtained to meet the FDA’s requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA; see Text Box 1). A new drug application/biological licensure application (NDA/BLA; for the FDA) or a marketing authorization application (MAA; for the EU) is a comprehensive submission of all relevant information required for a drug to be approved for marketing. At the time of approval, all of this information is summarized in the product labeling (SmPC for the EU), a document that describes in detail the most relevant information for the prescriber of the new drug, particularly, how to use the drug, in which patient population, and the safety profile of the product.

To submit an NDA (also known in the EU as a dossier), the sponsor must submit all documentation in the common technical document (CTD), including chapters such as: Efficacy/Safety and Toxicology, Chemistry Manufacturing Controls (CMC), Clinical Pharmacology, Statistics, and Clinical Study Reports; as well as clinical datasets ready for analysis. In the United States, after an NDA is submitted, FDA has 60 days to perform a “completeness check.” By day 74, the FDA issues a letter stating whether the NDA has been accepted for submission (filed) or not, and if filed, whether it will be subject to standard review or priority review (see below). The review time for priority and standard applications is 6 and 10 months, respectively. Of note, the review clock starts after filing acceptance. If a “refused to file” (RTF) letter is issued, the letter should contain the list of the major deficiencies and actions needed to correct the deficiencies.

For some NDAs, the Office of Hematology and Oncology Products (OHOP) may seek advice from an external panel of independent experts, also known as the Oncology Drug Advisory Committee (ODAC). At the ODAC, OHOP and sponsor representatives present the key nonclinical and clinical information under review to the panel, and OHOP leadership and reviewers pose specific questions to the panel to get advice on the safety, efficacy, and approvability of a product. OHOP may (or may not) follow this ODAC advice.

After the FDA has completed review of the NDA, there are two potential outcomes: (i) an approval letter or (ii) a complete response (CR) letter. The CR letter describes the deficiencies that the sponsor needs to correct before obtaining approval.

Finally, when the sponsor for a drug that is already approved in the United States pursues approval for another indication, the sponsor must submit a supplement to the NDA, also known as an sNDA.

EU

To submit a marketing authorization approval (MAA), the sponsor submits all documentation (CTD dossier), including nonclinical testing for efficacy/safety and toxicology, CMC, clinical pharmacology, and statistics and clinical study reports, similar to the FDA. The main difference between FDA and EU CTDs is that the FDA requires submission of raw data and derived datasets as it conducts its own analysis, whereas the EU CTDs relies more on the information presented in the summaries of efficacy and safety.

Almost all oncology drugs are submitted via the centralized procedure (CP).

Centralized procedure. The CHMP plays a vital role in the marketing procedures for medicines in the EU (9, 10). Once a letter of intent to file a dossier is submitted, the CHMP appoints a Rapporteur and a Co-Rapporteur. The role of the Rapporteur(s) is to perform the scientific evaluation and to prepare an assessment report to the CHMP in accordance with the timetable agreed upon for the evaluation procedure (210 calendar days until opinion excluding clock stop to allow for responses from the sponsor to CHMP questions and another 67 calendar days until official approval by the European Commission).

It is recommended that sponsors interact with European Medicines Agency (EMA) to discuss any procedural or regulatory issues on the proposed submission. The scientific opinion of the CHMP needs to occur before day 210. This is followed by a binding decision from the European Commission (EC). There are two potential outcomes: (i) either approval in all member states or (ii) a refusal to market the product in any EU member state. CHMP opinion requires a majority consensus from members. On critical topics, CHMP may request the independent advice/recommendations of the Scientific Advisory Group on Oncology (SAG-O). Although the SAG-O is comparable with the ODAC, SAG-O deliberations are not open to the public. SAG-O advice helps the CHMP members decide on an opinion.

Text Box 1. Goals of the NDA

1. To provide enough information to permit FDA reviewers to reach the following key decisions:
   i. Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
   ii. Whether the drug’s proposed labeling (package insert) is appropriate, and what it should contain.
   iii. Whether the methods used in manufacturing the drug and the controls used to maintain the drug’s quality are adequate to preserve the drug’s identity, strength, quality, and purity.
Moreover, the EU has another approval procedure known as approval based on exceptional circumstances (11): this occurs when applicants are unable to provide comprehensive data on efficacy and safety due to three exceptional circumstances: (i) rare disease indications, or (ii) in the present state of scientific knowledge, more comprehensive information cannot be provided, or (iii) it would be contrary to generally accepted principles of medical ethics to collect such information. Approval based on exceptional circumstances needs yearly reassessment (11).

Hartmann and colleagues analyzed the regulatory review patterns and the probability for approval for anticancer drugs in the United States and the EU and concluded that, on average, patients in the United States get access to new products earlier, most likely due to the more frequent use of expedited review procedures (12) such as priority review and accelerated approvals, based on single-arm studies and/or based on the use of surrogate markers of clinical benefit such as progression-free survival (PFS) or response rate. In contrast, in general, the EU approves agents based on randomized controlled trials using endpoints of clinical benefit such as overall survival, and uses conditional/exceptional approval or accelerated assessment (see below) less frequently.

Companion Diagnostic Development and Personalized Medicine

United States

Companion diagnostic development is the development of an IVD or test, which is to be used together with a drug to identify patients in the following situations: (i) patients who are most likely to benefit from a particular therapeutic product; (ii) patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product; and (iii) monitoring of response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness.

To validate an IVD, the sponsor needs to demonstrate the following: (i) analytical performance: the ability of the IVD to accurately and reproducibly select patients whose samples contain (or lack) the analyte(s) of interest (13, 14) and (ii) clinical performance: the ability of the diagnostic to select patients in a way that will improve the risk–benefit balance of the associated drug. To achieve this aim, it is often necessary to determine a priori a cutoff value that will differentiate patients into the desired outcome classifications, for example, responders versus nonresponders. It is expected that a novel IVD companion diagnostic should be approved or cleared contemporaneously (either before or at the time of drug approval) by the FDA for the use indicated in the labeling. For more in-depth discussion of companion diagnostic development, please refer to an article by Mansfield in this CCR Focus section (15). Examples of co-development IVDs include Her2 assay with trastuzumab, c-kit immunohistochemistry with imatinib, and EGFR receptor (EGFR) DNA mutations with afatinib and erlotinib (14).

EU

Before any IVD can be placed in the European market, it must meet the requirements of the relevant EU product directives, also known as Conformité Européenne “(CE) mark (16). The CE mark is the manufacturer’s declaration that its product complies with the required health and safety regulations. There are two ways to obtain the CE in the EU: (i) sponsor submission to an EU country, or (ii) a self-CE by the sponsor (17).

Recently, the EMA issued a new guidance for the qualification of novel methodologies for drug development, including biomarkers. This guidance describes how a sponsor can obtain a CHMP opinion on the acceptability of a specific use of the proposed method (18). Moreover, EMA is working on new legislation to harmonize the companion diagnostic requirements. For more in-depth information about the current and future European regulatory considerations for companion diagnostics, please refer to a review by Pignatti and colleagues in this CCR Focus section (19).

When we compare the regulations required for companion diagnostics in both the FDA and the EU, it is very clear that in the United States, the novel IVD to be used in a registration trial of a new drug must be approved before (or at the same time) the drug is approved to be marketed. In contrast, to use an IVD for marketing of a new drug in the EU, obtaining a CE for the IVD would suffice. There is not yet a requirement that a companion diagnostic be approved by EMA before or after a corresponding drug is approved. The advantage of developing a companion diagnostic before marketing a novel drug is that patients requiring a predictive IVD will be selected by a more stringent, accurate, and less variable single test, thus increasing the probability of drug success while sparing patients who may not benefit from the drug. The disadvantage is that it can lengthen the time to approval, unless development is started very early.

Expedited and Special Programs for Drug Approval

United States

The FDA has created several regulatory mechanisms to accelerate drug approvals in patients with serious conditions, such as advanced malignancies as well as certain nononcological diseases. These expedited programs are: fast track designation (FT), breakthrough designation (BT), accelerated approval (AA), and NDA priority review (Table 2 and Fig. 1). A new draft guidance for expedited programs for serious conditions was issued in June 2013. After comments are incorporated, this guidance will be final in 2014 (20).

**Fast-track designation and breakthrough designation.** As depicted in Fig. 1, fast-track (FT) and breakthrough (BT) designation occurs before NDA/BLA submission. In contrast, AA and priority review are part of the approval process. To qualify for FT or BT designation, a drug should be indicated for a serious condition that demonstrates the potential to address an unmet medical need and has preliminary evidence of significantly improved efficacy over existing available therapy. Please see Text Box 2 for
regulatory definitions for serious condition, available therapy, and unmet medical need.

Although there are many similarities between FT and BT designation, there are several distinctions. For instance, to qualify for FT, a drug needs to demonstrate the potential to address an unmet medical need with either preclinical or relevant clinical information. The features of FT designation include the following: (i) more frequent interaction with the review team and (ii) rolling review, meaning the submission of portions of an NDA before the sponsor submits the complete application, potentially shortening the review process. In contrast, BT designation requires that the drug have preliminary evidence of clinical activity with substantial improvement over existing therapies in one or more significant clinical endpoints, such as overall survival. BT not only has all of the FT features, but also intensive guidance of an efficient drug development program as early as phase 1 with involvement of senior managers and experienced review staff in a proactive collaboration.

As of December 20, 2013, there have been 123 total requests for BT, of which only 36 requests were granted and 69 requests were denied. Eleven of the 26 BT designations were in the field of oncology (21).

Accelerated approval. The FDA may grant accelerated approval to a product for a serious or life-threatening condition based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit and needs to be superior to available therapy. It is important to understand that accelerated approval still requires evidence of clinical benefit from confirmatory postapproval clinical trials. Lack of confirmation may lead to withdrawal of an indication or a drug from the market (20).

### Table 2. Types of drug approvals and expedited programs at FDA/EMA

<table>
<thead>
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<tbody>
<tr>
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<tr>
<td>Expedited programs</td>
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<td>Priority review</td>
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<tr>
<td>Accelerated assessment</td>
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<tr>
<td>Accelerated approval&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>No</td>
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<tr>
<td>Conditional approval&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>Yes</td>
</tr>
<tr>
<td>BT designation</td>
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<td>No</td>
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<tr>
<td>FT designation</td>
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<td>No</td>
</tr>
<tr>
<td>Rollover NDA</td>
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<td>No</td>
</tr>
<tr>
<td>Exceptional circumstances</td>
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<td>Yes</td>
</tr>
<tr>
<td>Companion diagnostics</td>
<td></td>
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<tr>
<td>Requirement of prior IVD approval for NDA</td>
<td>Yes</td>
<td>No</td>
</tr>
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<sup>a</sup>Need to demonstrate postmarketing evidence of clinical benefit.
<sup>b</sup>In the EU, conditional approval requires yearly renewal until full approval.

### Priority review. An application for a drug will receive a priority review designation if a drug treats a serious condition, and if approved, would provide a significant improvement in safety or effectiveness (the EU equivalent is accelerated assessment). A priority review designation means that the goal of the FDA is to take action on the NDA within 6 months (compared with 10 months under standard review).

### EU

Similarly, the EU has created regulatory mechanisms to accelerate drug approvals in patients with serious conditions. These expedited programs are: accelerated assessment and conditional approval (Table 2 and Fig. 1).

### Accelerated assessment. After the sponsor requests an accelerated assessment (EU equivalent for U.S. priority review) of the dossier, the Rapporteurs would advise the CHMP whether this request has major public health interest as well as therapeutic innovation. If the CHMP accepts the request, the timeframe for the evaluation will be reduced from 210 days to 150 days (9).

### Conditional approval. For certain categories of medicinal products, in patients with unmet medical needs and in the interest of public health, the CHMP will grant marketing authorizations based on less complete data than are normally required. A conditional approval may only be granted for products that fulfill an unmet medical need where the risk-
benefit balance is positive, it is likely that the applicant will be in a position to provide the comprehensive clinical data, and the immediate availability on the market outweighs the risk inherent in the fact that additional mature data are still required. Conditional approvals are reviewed annually. The conditions considered for conditional approval are serious debilitating diseases or life-threatening diseases, products to be used in emergency situations, or products designated as orphan medicinal products. However, timelines for approval based on conditional approval is similar to the traditional approval (22). As of September 2013, according to the EMA web page, about 10 new drugs received conditional approval.

Of note, in Europe there are ongoing discussions on potential “adaptive licensing” (similar to BT in the United States), potentially allowing shorter approval times (23).

Thus, there are several differences between the EU and United States with respect to expedited programs for drug approvals. At press time, in the United States, two oncology products, obinutuzumab, for the treatment of chronic lymphocytic leukemia, and ibrutinib, for the treatment of mantle cell lymphoma already received approvals with BT designation. Of note, same requirement for prior clearance for the IVD is also applicable for BT. One important distinction with the EU is that in the United States, accelerated approvals are based on a surrogate likely to provide clinical benefit. However, in the EU, conditional approval does not depend on the endpoint evaluated, but on the “less complete data” required for approval, and this conditional approval requires annual review to continue in the market.

Examples of Drug Approvals

In this section, we provide examples that demonstrate different approaches taken by the FDA and EMA based on the same available information. First, erlotinib approval for advanced/metastatic pancreatic cancer is an example of significant labeling indication differences in the EU and in the United States. Second, approval of panitumumab for advanced colorectal carcinoma represents an initial drug approval that required narrowing of the indication based on information obtained retrospectively with an IVD. The third example is gefitinib approval for treatment in non–small lung cancer. Gefitinib was initially approved by the United States in 2003 using the accelerated approval procedure that, in subsequent trials, failed to demonstrate clinical benefit in the same population, leading to its withdrawal from the U.S. market. However, the sponsor gained European approval through a submission based on a biomarker. Each of these examples represents decisions based on the absence of a validated companion diagnostic, and it could be argued that the absence of an IVD led, at least in part, to a discordance between the regulatory bodies.

**Erlotinib for advanced pancreatic carcinoma**

*United States.* The drug sponsor, OSI Therapeutics, in collaboration with the National Cancer Institute of Canada, conducted a phase III trial of erlotinib (a drug already approved for the treatment of lung cancer) in combination with gemcitabine versus gemcitabine plus placebo in patients with locally advanced or metastatic adenocarcinoma of the pancreas. Although there was a statistically significant increase in overall survival, the median increase in the experimental arm was less than 2 weeks longer than that in the control arm (24). Furthermore, the combination of gemcitabine plus erlotinib demonstrated significantly higher toxicity (24). Because of the modest survival improvement and increase in toxicity observed in this trial, this application was discussed at the ODAC meeting in September 2005. ODAC voted in favor of approval (10 yes and 3 no). The FDA followed the advice of ODAC and approved the supplemental NDA in November 2005 in both locally advanced and metastatic disease, the population studied in the phase III trial (24, 25).

**EU.** Despite the statistically significant increase in survival for the combination gemcitabine and erlotinib, CHMP refused the type II variation (equivalent to sNDA in the United States) due to the clinically insignificant increase in survival in the context of an increase in toxicity. The sponsor requested a reexamination and the CHMP appointed new Rapporteurs. In December 2006, the CHMP reconsidered this negative opinion and recommended by a majority that its initial opinion should be revised, accepting a more restricted indication, metastatic pancreatic cancer only, where the difference in median overall survival was greater as compared with the locally advanced, unresectable pancreatic cancer setting. Thus, erlotinib was approved in metastatic pancreatic cancer alone, based only on a retrospective subgroup analysis of the subgroup with metastatic disease from the phase III pivotal trial (24, 26).

**Panitumumab for advanced colorectal carcinoma**

*United States.* Panitumumab is a humanized monoclonal antibody that binds specifically to the human EGFR. As part of the NDA submission, the sponsor submitted a single, open-label, multicenter trial in which 463 patients with EGFR-expressing metastatic colorectal carcinoma who had disease progression on or following treatment with a regimen containing a fluoropyrimidine, oxaliplatin, and irinotecan were randomized (1:1) to receive best supportive care with or without panitumumab. Although median PFS was similar in both treatment arms (~8 weeks), the mean PFS was approximately 50% longer among patients receiving panitumumab. No difference in overall survival was observed.

Panitumumab received accelerated approval in 2006 based on PFS improvement, an endpoint considered a surrogate likely to provide clinical benefit. However, new clinical data following approval demonstrated a lack of efficacy of EGFR-directed antibodies in patients with metastatic colorectal carcinoma KRAS mutation; the FDA convened an ODAC panel, which concluded that anti-EGFR monoclonal antibodies were not effective in patients with KRAS-mutant metastatic colorectal carcinoma. Unfortunately, at the time of this ODAC, there was not an FDA-approved K-Ras IVD. Despite the lack of an approved IVD, on July 17, 2009, the FDA restricted the use of anti-EGFR monoclonal antibodies, cetuximab and panitumumab, only to patients with wild-type KRAS metastatic colorectal carcinoma (27). Of note, the first KRAS IVD was approved in July 2012.
EU. In May 2007, CHMP after consultation with SAG-O issued a negative opinion for granting marketing approval to panitumumab. This opinion was based on the lack of meaningful benefit and a negative benefit–risk ratio for panitumumab in this setting. The applicant submitted a written notice to the EMA to request a reexamination of the dossier. New Rapporteurs were appointed to prevent bias from the initial CHMP assessment. CHMP SAG-O experts were consulted for reexamination. Finally, during the September 2007 meeting, the CHMP recommended the approval of panitumumab using the conditional approval mechanism. This change in opinion followed the submission of clinical data relevant to the KRAS status. The approval was based on a positive benefit–risk ratio in the restricted population (wild-type KRAS metastatic colorectal carcinoma tumors). As part of the conditional approval, the sponsor was required to make a postmarketing commitment to understand the clinical interaction between panitumumab and KRAS mutation in metastatic colorectal carcinoma (28). There was no formal EMA approval for the KRAS diagnostic assay required for this indication.

Gefitinib in patients with NSCLC

United States. In May 2003, gefitinib received accelerated approval by the FDA as monotherapy for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. (29). The approval was based on a single-arm trial of two oral doses of gefitinib (250 vs. 500 mg/day). A total of 216 patients were enrolled with an overall response rate (primary endpoint) of 10.6% and a median duration of response of 7.0 months. In two postmarketing trials, gefitinib failed to demonstrate an increase in overall survival. Thus, gefitinib was withdrawn from the market (30). As of the time of this writing (December 2013), gefitinib is still not available in the United States.

EU. In February 2003, the sponsor submitted the marketing approval application for gefitinib for the treatment of NSCLC. In January 2005, the sponsor withdrew the application and submitted a new marketing approval application based on two large phase III trials in unselected patients with NSCLC: ISEL (N = 1,692) and INTEREST (N = 1,466). The primary endpoint for these trials, overall survival, was not improved by the addition of gefitinib (31). However, based on novel information about the potential mechanism of action for EGFR tyrosine kinase inhibitors, the sponsor submitted a retrospective analysis of available tumor samples, correlated with clinical data. EGFR mutation information was available in approximately 20% of all treated patients: EGFR mutation was detected in 12% and 15% of these samples in the two trials, respectively. A retrospective subgroup analysis revealed a significant increase in response rate and PFS without an increase in overall survival in patients with EGFR-mutant NSCLC (31). Gefitinib was approved by the EMA for patients with NSCLC with activating mutations of EGFR. IVD approval was not required for gefitinib approval.

As noted above, each of these examples highlights the problems that arise in the interpretation of data obtained in the absence of a validated biomarker before approval. In case 1, a biomarker was not available, and, in the second and third case, biomarkers were found but were determined and analyzed retrospectively from subgroup analysis, leading to different outcomes in different regions. Together, these examples and those discussed elsewhere in this CCR Focus section (31) show how important it is to perform a prospective study using a validated predictive IVD that has been developed early in the drug approval process. As soon as a subpopulation that may benefit from a drug has been identified, efforts should be made to test this prospectively with a validated IVD required for study entry to determine the true validity of the IVD and drug benefit in this population.

Summary

The drug approval processes and requirements are somewhat different in the United States and the EU. One of the most significant differences is with respect to companion diagnostic development requirements. Companion diagnostic development requirements are more stringent in the United States than the EU, and therefore likely to be accepted by CHMP. Fortunately, health authorities are actively working on implementing standards to harmonize both regions. In summary, sponsors should be aware of the dynamic regulatory environment and always consult the health authorities when in doubt.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: A.M. Senderowicz, O. Pfaff
Development of methodology: A.M. Senderowicz, O. Pfaff
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Senderowicz
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Senderowicz, O. Pfaff
Writing, review, and/or revision of the manuscript: A.M. Senderowicz, O. Pfaff
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.M. Senderowicz, O. Pfaff
Study supervision: A.M. Senderowicz

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Similarities and Differences in the Oncology Drug Approval Process between FDA and European Union with Emphasis on In Vitro Companion Diagnostics

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