Post-Marketing Requirements for Cancer Drugs Approved by the European Medicines Agency, 2004–2014

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To address unresolved questions about drug safety and efficacy at the time of approval, the European Medicines Agency (EMA) may require that manufacturers conduct additional studies during the postmarketing period. As a growing proportion of new cancer drugs are approved on the basis of limited evidence of clinical benefit, timely completion of postmarketing requirements is important. We used publicly available regulatory documents to evaluate key characteristics of pivotal studies supporting EMA-approved cancer drugs from 2004–2014 and assessed completion rates of postmarketing data collection requirements after a minimum of 5 years. From 2004–2014, 79% (45/57) of EMA-approved cancer drugs had to fulfill postmarketing requirements. Pivotal trials supporting the approval of cancer drugs with postmarketing requirements were less likely to have randomized designs (41/61, 67% vs. 11/11, 100%), include an active comparator (20/61, 33% vs. 10/11, 91%), or measure overall survival as the primary study end point (18/61, 30% vs. 6/11, 55%) compared with pivotal trials for drugs without postmarketing requirements. Among 200 postmarketing requirements, almost half were designed to assess drug safety. After a minimum of 5 years, 60% (121/200) of requirements were completed, 10% (19/200) were ongoing, and 30% (60/200) were delayed. About half (40/75, 53%) of postmarketing requirements for new clinical studies were completed on time. Delays in the completion of postmarketing requirements often did not impact the likelihood of drugs receiving permanent marketing authorization (87%, 39/45) after 5 years. Our findings highlight the need for EMA to better enforce its authority to require timely completion of postmarketing requirements and studies.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ A growing number of new cancer drugs in Europe are approved based on limited clinical trial data and may be required to address unresolved questions about drug safety and efficacy through postmarketing requirements.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Using regulatory documents, we characterized the design and completion of postmarketing requirements for cancer drugs approved by the European Medicines Agency (EMA). We also examined whether the completion of postmarketing requirements influenced regulatory decisions for permanent authorization.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ From 2004 to 2014, the EMA assigned postmarketing data collection requirements to four-fifths of newly approved cancer drugs. More than one-third of postmarketing requirements were ongoing or delayed after at least 5 years, including about one-half of requirements for new clinical studies. Despite delays in the completion of postmarketing requirements, this often did not impact the likelihood of temporarily authorized drugs receiving permanent marketing authorization.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ European regulators should work with manufacturers to develop postmarketing research plans that address limitations in the available evidence and improve compliance with study timelines.

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The European Medicines Agency (EMA) is responsible for evaluating the benefits and risks of new drugs before they can be prescribed in the European Union. As part of the regulatory approval process, drug manufacturers conduct clinical trials to demonstrate that their products have sufficient safety and efficacy and that the benefits outweigh the risks. To address unresolved questions about new drugs at the time of approval, the EMA may require that manufacturers conduct additional studies during the postmarketing period. When postmarketing requirements have been delayed or have not been fulfilled, the EMA can send a letter to the manufacturer, request an oral explanation, request an inspection, or vary, suspend, or revoke marketing authorization.[1]

Since 2004, the marketing authorization of all new drugs approved by the EMA and drugs authorized under exceptional circumstances ("when comprehensive data cannot be obtained even after authorization") is valid for 5 years, whereas drugs with conditional marketing authorization are renewed yearly. Prior to the initial marketing authorizations' expiration, manufacturers may be required to submit postapproval data to validate safety and efficacy and resolve outstanding uncertainty before permanent marketing authorization may be granted. For instance, drugs granted conditional marketing authorization are required to conduct postmarketing studies to confirm a positive risk–benefit ratio. Postmarketing studies can generate essential information on drug benefits and harms.[2] Such studies typically generate additional data on dosing, safety, and real-world effectiveness.[3–5] However, compliance with postmarketing requirements often lacks enforcement[6] and delays in study timelines are frequent.[7–11]

Cancer drugs comprise the largest category of drugs with postmarketing requirements.[9,11] This is because evidence on the efficacy and safety of cancer drugs is often limited at the time of regulatory approval. In Europe, most new cancer drugs are approved based on changes to surrogate measures and without evidence on clinical outcomes, such as quality of life or overall survival.[12,13]

Previous studies have examined the completion of postmarketing requirements for drugs with conditional marketing authorization in Europe.[8,9] However, drugs with conditional marketing authorization account for a minority of new drug approvals with postmarketing requirements. In this study, we characterized postmarketing requirements for cancer drugs approved in Europe from 2004–2014 based on public information reported in European regulatory documents. We compared the characteristics of preapproval clinical trials for drugs with and without postmarketing requirements. Additionally, because drugs seeking to remain on the market after 5 years are required to apply for permanent marketing authorization, we examined whether the completion of postmarketing requirements influenced regulatory decisions for permanent authorization.

METHODS

Cohort identification

We used the EMA website to identify new molecular entities with an anatomic therapeutic chemical classification code covering antineoplastic and immunomodulating agents (L01) approved from 2004–2014. We excluded generics, non-therapeutic agents, pediatric indications, and supplemental indication extensions of existing drugs ("type 2 variations").

Identification of postmarketing requirements

We identified postmarketing requirements from European public assessment reports at the time of first marketing authorization and from annual or 5-year renewal assessment reports. Postmarketing requirements are included in the "summary of product characteristics" or listed in the risk management plan along with the details and anticipated completion dates of these requirements. At the 5-year mark, the EMA decides based on the submitted evidence whether to grant permanent marketing authorization or request further data for safety or efficacy ("grounds for one additional renewal").[14,15]

We accessed European public assessment reports corresponding to renewal assessment dates published until December 31, 2019, via the European Union register of medicinal products for human use.[16] If the public assessment report corresponding to the renewal assessment date was unavailable, the most recent complete assessment following the renewal was used, such as the modification, corrigendum, or variation assessment report. We extracted requirements relating to the collection of additional data on efficacy or safety from public assessment reports. We excluded "routine pharmacovigilance activities," but included pharmacovigilance studies specifically requested in the risk management plan as non-routine activities or when they were affiliated with another postmarketing requirement (e.g., collection of pharmacovigilance data from an ongoing or requested study). Two investigators (authors A.C. and M.S.K.) independently extracted data for postmarketing requirements and the marketing authorization status for half of drugs to ensure high internal agreement. Differences were resolved through discussion and consensus among the investigators.

Status of postmarketing requirements

We used multiple publicly available regulatory documents to verify the completion of postmarketing requirements. This included renewal assessments available through the European Union register of medicinal products for human use, the summary of product characteristics, which includes a detailed clinical summary of information for each approved drug, and the "procedural steps taken and scientific information after the authorization" from the European public assessment report, which details changes that are introduced after the initial marketing authorization.

The status of postmarketing requirements was categorized as of December 31, 2019, according to the following criteria: first, if postmarketing requirements from the initial approval or subsequent renewal assessments were removed from the risk management plan or the list of conditions for granting marketing authorization, we categorized these as completed. We also categorized requirements as completed if new information was added to the summary of product characteristics that appeared to indicate that the requirements had been fulfilled. Second, if requirements were not yet complete but still within the timeframe requested by the EMA, these were categorized as ongoing. If there was no prespecified date of completion in the risk management plan and the requirements were not yet complete by the end of our study period, we categorized these as ongoing. Third, if postmarketing requirements had passed the requested timeframe and were not completed, or if the initial timeframe had been extended, we categorized these as delayed. Detailed examples of how we categorized postmarketing requirements are provided in **Box S1**.

Objective of postmarketing requirements

Postmarketing requirements were categorized as follows: efficacy (tumor response or disease progression, overall survival, or quality of life), safety (pharmacovigilance), pharmacokinetics and pharmacodynamics, dosing, or others. When the study objective was not specified or was not clearly identifiable based on key terms (e.g., efficacy, safety, dosing, and pharmacokinetics), we categorized these requirements as relating to efficacy and safety.

Characteristics of clinical trials

We also documented the characteristics of pivotal studies and postmarketing requirements. Design features included treatment allocation (randomized or single arm), blinding (double-blind, single blind, or open label), comparators (active, placebo, self, none), enrollment, and the primary study end point. Features not included in regulatory documents were verified by searching ClinicalTrials.gov.

Marketing authorization status

New drugs approved by the EMA are initially authorized under a temporary license lasting 5 years. This can be converted to permanent authorization if postapproval data confirms the safety and efficacy of the drug and resolves uncertainty associated with the initial evidence submission. We investigated if and when the initial marketing authorization status of cancer drugs was updated by searching the "procedural steps taken and scientific information after the authorization" in the public assessment report, and the summary of product characteristics in the European Union register of medicinal products for human use for entries corresponding to the renewal of the marketing authorization status.

RESULTS

From 2004 to 2014, the EMA approved 56 new cancer drugs. Forty-two (75%) were approved via a special regulatory program. Twenty-five (45%) of these were approved for rare diseases, whereas 12 (21%) received conditional marketing authorization.

Collectively, 72 pivotal trials supported approval of the 56 cancer drugs. Approximately three-quarters were randomized (52/72, 72%) and 42% used an active comparator (30/72). Most trials used surrogate measures such as tumor response or time-to-progression (29/72, 40%), or progression-free survival (19/72, 26%), as the primary end point. Among the 24 trials with overall survival as the primary (or co-primary) end point, the median improvement was 2.4 months (interquartile range (IQR): 1.4–3.8).

Among the 56 cancer drugs approved from 2004–2014, 45 (80%) were required to fulfill postmarketing requirements.

Table 1 Characteristics of cancer drugs approved with and without postmarketing requirements

Characteristics	Drugs with postmarketing requirements	Drugs without postmarketing requirements
Drugs	45	11
Special regulatory program		
Accelerated assessment	2 (4)	0
Conditional marketing authorization	12 (27)	0
Exceptional circumstances	4 (9)	0
Rare disease	21 (47)	3 (27)

Data are numbers (%). Drugs can be approved through more than one special regulatory program.

Twenty-one (47%) drugs approved with postmarketing requirements received a rare disease drug designation compared with two drugs (27%) without postmarketing requirements. Additionally, 12 (27%) drugs with postmarketing requirements received conditional marketing authorization (**Table 1**).

Pivotal trials supporting the approval of cancer drugs with postmarketing requirements compared with pivotal trials for drugs without requirements were less likely to have randomized designs (41/61, 67% vs. 11/11, 100%), include active comparators (20/61, 33% vs. 10/11, 91%), or measure overall survival as the primary study end point (18/61, 30% vs. 6/11, 55%; **Table 2**).

Objectives and characteristics of postmarketing requirements

We identified 200 postmarketing requirements for the 45 cancer drugs. The median number per drug was 3 (IQR 2–6). **Table 3** shows the most common objective was for the evaluation of safety

Table 2 Comparison of pivotal trial characteristics

Trial characteristics	Pivotal trials for drugs with post-market requirements (n = 61)	Pivotal trials for drugs without post-market requirements (n = 11)
Study enrollment, median (IQR)		
Total	416 (140–760)	448 (337–591)
Intervention	254 (110–454)	242 (222–322)
Randomized	41 (67)	11 (100)
Double-blind	20 (33)	1 (9)
Comparator		
Active	20 (33)	10 (91)
Placebo	19 (32)	1 (9)
Self	2 (2)	0
None	20 (33)	0
Primary study end point[a]		
Overall survival	18 (30)	6 (55)
Progression-free survival	14 (23)	4 (36)
Other surrogate	29 (48)	1 (9)

Data are numbers (%) unless stated otherwise. Pivotal trial characteristics for mitotane were not available from European public assessment reports or ClinicalTrials.gov and were not included in the total number of pivotal trials.
IQR, interquartile range.
[a]Pivotal trials which had overall survival and a surrogate measure as co-primary end points were categorized as survival.

Table 3 Characteristics, status, and objective of cancer drugs approved by the European Medicines Agency with postmarketing requirements, 2004–2014

Characteristics	No. (%) of drugs or requirements
Postmarketing requirements per drug	
1	11 (24)
2	8 (18)
3	8 (18)
4	2 (4)
≥5	16 (36)
Objective of postmarketing requirements	
Safety	94 (47)
Efficacy and safety	51 (25)
Efficacy	35 (18)
Other[a]	6 (3)
Safety and pharmacokinetics	6 (3)
Pharmacokinetics	3 (2)
Safety, pharmacokinetics, and dosing	2 (1)
Efficacy, safety, and dosing	2 (1)
Efficacy, safety, pharmacokinetics, and dosing	1 (1)
Status of postmarketing requirements	
Completed	121 (60)
Ongoing	19 (10)
Delayed	60 (30)

[a]Other refers to statistical analysis plans, testing kits or assay development.

Table 4 Information on the characteristics of postmarketing study requirements from regulatory documents

Trial characteristics	No. (%)
Postmarket study requirements	75 (100)
Study enrollment	7 (9)
Median (IQR)	85 (62.5–109)
Treatment allocation	50 (67)
Randomized	12 (24)
Single arm	38 (76)
Blinding	51 (68)
Double-blind	3 (6)
Single-blind	1 (2)
Open label	47 (92)
Comparator	52 (69)
Active	9 (17)
Placebo	0
Self	3 (6)
None	40 (77)
Primary study end point	28 (37)
Overall survival	4 (14)
Progression-free survival	3 (11)
Other surrogate	12 (43)
Safety	9 (32)

Data are numbers (%) unless stated otherwise. Study descriptions did not routinely include information on design characteristics such as randomization (50/75, 67%), blinding (51/75, 68%), comparators (52/75, 69%), end points (28/75, 37%), patient enrollment (7/75, 9%), or study duration (5/75, 7%). IQR, interquartile range.

(94, 47%). The complete list of postmarketing requirements is provided in **Table S2**.

Most postmarketing requirements (125/200, 62%) were for retrospective secondary analyses or data from ongoing clinical trials. Fourteen drugs had only retrospective data collection requirements, whereas the remaining 31 were associated with 75 prospective postmarketing studies. Nine of the 31 drugs with requirements for new clinical studies were approved with conditional marketing authorization. Among 75 prospective postmarketing studies requested by the EMA, 72% (54/75) detailed interventional studies (clinical trials in which patients were to be assigned to an intervention via randomized or non-randomized allocation) and 28% (21/75) observational studies (pharmacovigilance studies, registries, cohort studies, and case–control studies).

Information on the design characteristics of postmarketing studies is presented in **Table 4**. Among interventional study requirements for drugs with conditional marketing authorization, 19% (5/27) included requirements for randomized allocation of treatments, 7% (2/27) for double-blinding, 15% (4/27) for using an active comparator, and 4% (1/27) for including overall survival as the primary study end point.

Status of postmarketing requirements

Figure 1 shows the status of postmarketing requirements. After a minimum of 5 years (and median of 8), 121 of 200 (60%) requirements were completed, 19 (10%) were ongoing, and 60 (30%) were delayed. Two-thirds (30/45, 67%) of cancer drugs had postmarketing requirements that were ongoing or delayed, whereas 38% (17/45) had multiple requirements that were ongoing or delayed.

About half (40/75, 53%) of postmarketing requirements for new clinical studies were completed on time and 33% (25/75) were delayed. Postmarketing requirements for new studies were completed at a lower rate than those for secondary analyses or collection of follow-up data from existing studies (40/75, 53% vs. 81/125, 65%). Of these, a higher proportion of observational studies (13/21, 62%) were completed compared with interventional studies (27/54, 50%).

A higher proportion of postmarketing requirements were completed among cancer drugs approved between 2004 and 2009 (65/91, 71%) vs. 2010 and 2014 (56/109, 51%). Postmarketing requirements with only a safety objective had higher rates of completion (67/94, 71%) compared with requirements for only efficacy (18/35, 51%), and for efficacy and safety (22/51, 43%).

Marketing authorization status

By the end of the study period, the EMA granted 87% (39/45) of cancer drugs with postmarketing requirements permanent marketing authorization. **Figure 2** shows that among the 30 drugs with ongoing or delayed requirements, 80% (24/30) received

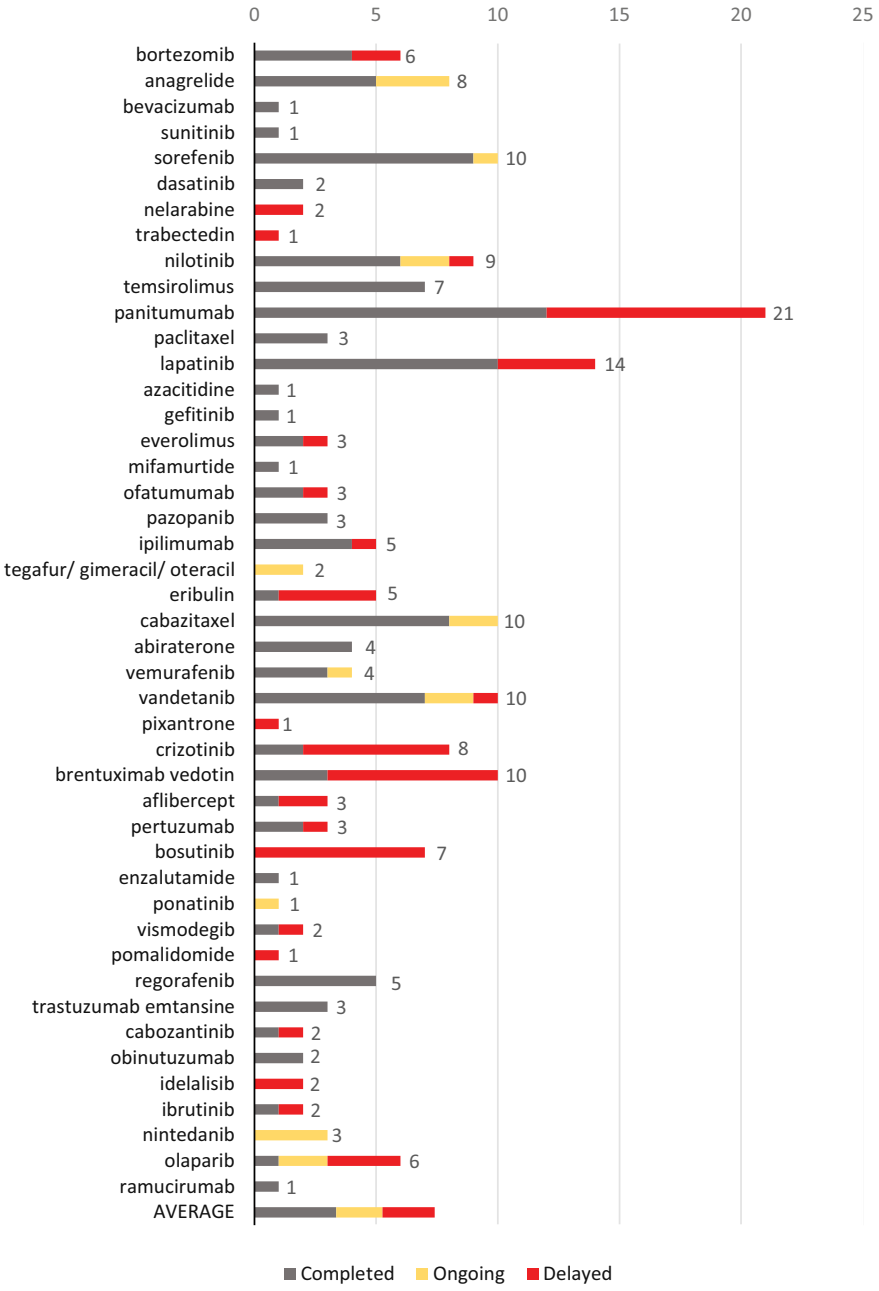

Figure 1 Postmarketing requirements fulfilled after a median 8 years. Total number of postmarketing requirements are listed beside each drug.

permanent marketing authorization. Of the six drugs (20%) without permanent authorization, three were renewed for conditional marketing authorization (vandetanib, bosutinib, and cabozantinib), two were required to submit an additional renewal assessment based on anticipated data from postmarketing requirements (cabazitaxel and idelalisib), and one was withdrawn by the manufacturer (ofatumumab).

DISCUSSION

This review of postmarketing requirements for cancer drugs approved by the EMA from 2004–2014 found that more than one-third were ongoing or delayed after at least 5 years of follow-up according to information available from European regulatory documents. Despite some unfulfilled obligations, most drugs given initial temporary status were converted to permanent marketing authorization. These findings highlight shortcomings in the timely fulfillment of postmarketing requirements, which are particularly important for cancer drugs that often lack robust evidence of clinical benefit at the time of approval.

Our study shows that postmarketing requirements for many cancer drugs were ongoing or delayed after several years on the European market. Only about half of postmarketing requirements for new clinical studies were completed on time. As new cancer drugs are increasingly approved on the basis of changes to

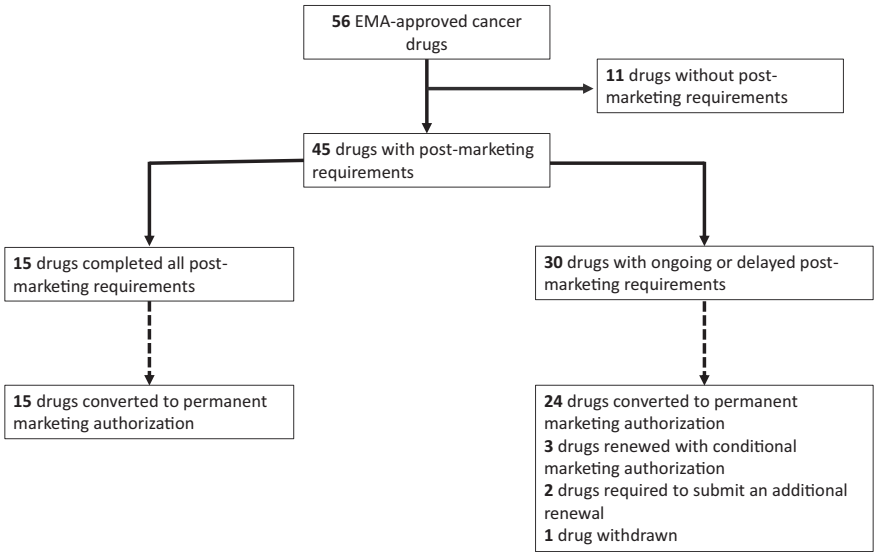

Figure 2 Fulfillment of postmarketing requirements and conversion to permanent marketing authorization. EMA, European Medicines Agency.

surrogate measures, postmarketing studies are essential to generate data on drug benefits and harms. Evidence generated during the postmarketing period may alter how the drug is prescribed, such as contraindications, restricted patient populations, safety communications, and boxed warnings.[4,5] Therefore, timely completion of these requirements is essential for informing clinical practice.

We found that most cancer drugs were converted to permanent marketing authorization despite ongoing or delayed postmarketing requirements. European public assessment reports did not routinely reference the status of these requirements in approval decisions, which further demonstrates a lack of enforcement from European regulators in postmarket data collection.[8,9,17]

Another finding from our study relates to the design of pivotal studies. Compared with cancer drugs without postmarketing requirements, cancer drugs with postmarketing requirements were often approved on the basis of non-randomized studies, placebo comparators, and surrogate measures. In view of this, regulators may design postmarketing requirements to address uncertainties associated with pivotal studies. However, publicly available information on postmarketing requirements often did not include key information about study designs. Greater consideration should be given to developing postmarketing research plans that directly correspond to limitations in the available evidence at the time of approval.

Comparison to other studies

Our findings confirm and extend the findings of earlier studies. In the United States, completion and public reporting of postmarketing studies is frequently ongoing or delayed.[7,10,11,18,19] This is also consistent for drugs with conditional marketing authorization in Europe.[8,9] Our study extends the latter analyses and finds that timely completion across all postmarketing requirements for EMA-approved cancer drugs is lacking.

Policy implications

Our findings highlight the need to improve postmarketing evidence generation in Europe in several ways. First, regulators and manufacturers should work together to develop postapproval research plans that address gaps in knowledge about a drug's benefits or risks. For example, drugs that receive EMA approval on the basis of single-arm studies should be required to validate drug benefits in randomized controlled trials during the postmarketing period.[2] Second, postmarketing requirements should be fully integrated within the European clinical trials registry to ensure transparency about the status and outcomes of these studies. Third, regulators should enforce their existing authority and require the completion of postmarketing requirements within agreed upon timelines. Reasons for delays in the completion of postmarketing requirements may be multifaceted.[20] For example, patient accrual can be slow because there is little incentive for most patients to participate in a clinical trial after a drug is approved for sale in Europe. In addition, protocol amendments may delay the initiation of a trial. Additional transparency from the EMA investigating the reasons for delays can help inform future policy decisions.

Limitations

The primary focus of our study was to identify information on postmarketing requirements using publicly available European regulatory documents. Therefore, it is possible that if additional requirements were requested by the EMA but omitted from regulatory documents, or if requirements were completed but not removed from regulatory documents, this would have influenced our results. Second, our categorization of postmarketing requirements was based on qualitative data synthesis, but we used prespecified criteria and confirmed difficult cases among multiple investigators to ensure high internal agreement and methodological consistency. Third, we were unable to determine specific dates

for status updates to postmarketing requirements. Fourth, our sample consisted of novel drug approvals and may not be generalizable to postmarketing requirements for supplemental indications added to already-approved drugs.

Finally, there is a possibility that the regulator and manufacturer can agree to the release of a postmarketing requirement if the study is no longer scientifically meritorious or has been answered by previous studies.[7,19,21] However, this should be clearly disclosed in regulatory documents, which was not the case for any of the drugs in our sample.

CONCLUSIONS

More than one-third of postmarketing requirements for cancer drugs approved by the EMA from 2004 to 2014 were ongoing or delayed after at least 5 years, including about one-half of new clinical studies. Despite unfulfilled obligations, most drugs were converted to permanent marketing authorization. European regulators should work with manufacturers to develop postmarketing research plans that address limitations in the available evidence and improve compliance with study timelines.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

The authors declare no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.C., E.M., M.S.K., A.S.K., and H.N. wrote the manuscript. A.C., E.M., M.S.K., A.S.K., and H.N. designed the research. A.C. and M.S.K. performed the research. A.C. and M.S.K. analyzed the data.

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