Follow-Up of Specific Obligations Required for Conditionally Authorized Anticancer Medicinal Products by the European Medicines Agency in 2006-2021: An In-depth Analysis

Narjisse Jagoui, 3-2-2023
Supervisors: Nancy Breekveldt-Postma, Lourens Bloem

Abstract

Background: The European Medicines Agency (EMA) has implemented a regulatory pathway for the conditional marketing authorization (CMA) of medicinal products. This pathway aims to facilitate timely patient access to treatments for unmet medical needs by accepting less comprehensive data than otherwise required. To obtain a CMA, the applicant must demonstrate a positive benefit-risk balance, fulfilment of unmet medical needs and likelihood that comprehensive data will be submitted post-authorization, and the immediate availability of the product must outweigh the risks associated with non-comprehensive data. To ensure that comprehensive data concerning safety and efficacy are obtained, specific obligations for post-authorization data submission are implemented that are reviewed yearly during annual renewal of the CMA.

Aim: The aim of this study was to investigate the follow-up of specific obligations required for anticancer medicinal products granted a CMA, including their duration, potential changes, and reasons for these changes.

Methods: A retrospective cohort study of specific obligations for anticancer medicinal products granted a CMA between 2006 and 2021 was performed. Data were extracted from the European Commission's Union Register of medicinal products and confidential EMA assessment reports. The state of specific obligations over time was investigated by following them up from initial authorization until they were fulfilled, the CMA was revoked, or the end of the study period (November 2022). The state of specific obligations was determined by comparing the wording at initial authorization and each follow-up moment (mostly annual renewals) and defined as maintained, fulfilled or changed. Changes were categorized as changes in due date, changes in description, or both.

Results: From 2006 to 2021, 40 anticancer medicinal products were granted a CMA. These products were subject to 92 specific obligations, which were followed for a median 2.5 years (IQR: 1.6-4.4), with the longest follow-up time being 10.7 years for Caprelsa. During follow-up, 245 states were determined. Of these, 140 (57%) comprised maintenance of the specific obligation, 28 (11%) change in due date, 7 (3%) changes in description, 6 (2%) changes in both due date and description and 63 (26%) obligations were fulfilled. Reasons for a change in due date were often enrolment delay. Major changes in description of the SOB were made for Tyverb and Xalkori. Major changes to the marketing authorization were also identified for Caprelsa and Rubraca, leading to a restricted indication of the CMA. Most of the SOBs (67%) with a due date delay of ≥3 years were granted a CMA in 2006-2012. After 2016 no major delays in due date were found at the end of follow-up, the CMA of 24 (60%) anticancer medicinal products were converted to a standard marketing authorization while 1 (3%) was revoked.

Conclusion: In conclusion, despite changes occurring in specific obligations, overall, most of time specific obligations are fulfilled as imposed and within the initially imposed due date. Especially in later years, only few major delays in due date (delay three years or more)/and or description occurred. Also, the time for a CMA to be converted to a standard marketing authorization decreased over time .This suggests that the current systems and procedures in place for managing conditional marketing

authorizations are effective in ensuring the ongoing safety and efficacy of these products and may have been become better overtime.

Introduction

The European Medicines Agency (EMA) has three regulatory pathways to authorize a new medicinal product in the European Union (EU): standard marketing authorization (MA), authorization under exceptional circumstances and conditional marketing authorization (CMA). For a standard MA, the applicant should submit comprehensive efficacy and safety data to support the assessment of the benefit-risk balance. In case of an authorization under exceptional circumstances, providing comprehensive data may not be possible because of a rare disease, because collection of full information is not possible or because collecting these data would be unethical.(1)(2) [1] In contrast, CMA can be granted based on less comprehensive data to provide early access to medicines that treat diseases with an unmet medical need. There are four criteria that should be met to be granted a CMA by the EMA's Committee for Medicinal Products for Human Use (CHMP): the benefit-risk balance of the medicine is positive, it is likely that the applicant will be able to provide comprehensive data post-authorization, the medicine fulfils an unmet medical need and the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.(3)[2]

Because initial submitted data are less comprehensive, there is a higher degree of uncertainty for medicinal products granted CMA compared to standard MA. To resolve uncertainties about efficacy, safety and quality and to confirm that the benefit-risk balance remains positive, the marketing authorization holder (MAH) is required to submit data of certain studies post-authorization, so-called *specific obligations*. Once granted a CMA, the authorization is valid for one year and can be renewed annually after re-assessment of the benefit-risk balance and the progress in fulfilling the specific obligations. After fulfilling all specific obligations and confirming that the benefits of the medicinal product still outweighs its risks, CMA will be converted into standard MA that is no longer subject to specific obligations. In case of a negative benefit-risk balance, the CMA can be suspended or revoked.(4)(5)[3,4] In contrast to specific obligations, which must be fulfilled in order for a standard marketing authorization to be granted, annex II conditions (ANX) are additional post-authorization measurements that do not affect the approval of a marketing authorization and can apply for both CMAs and standard MAs. These studies also play an important role in the benefit/risk balance of a medicinal product.(6)[5]

Previous studies showed that during follow-up changes in specific obligations can occur. These changes mainly consist of change in due date and changes in (text) description.(7)(8)[6,7] While other studies have examined the outcomes of the process between firms and regulators, the focus of this study is to investigate the changes that occur in specific obligations within the process. Specifically, this study aims to investigate the follow-up of specific obligations required for anticancer medicinal products granted a CMA, including their duration, potential changes, and reasons for these changes.

Methods:

Study design and cohort selection

We performed a retrospective cohort study of specific obligations imposed as a condition to the CMA of anticancer medicinal product authorized from January 2006 to December 2021 in the EU. The CMAs and there SOBs were identified in the Union Register of medicinal products for human use of the European Commission.(9)[8] Initial descriptions and due dates of specific obligations at time of

authorization were accessed through the EC Community Register of medicinal products and extracted from Annex II to the CMA.

Cohort characterization

For the includes medicinal products, we collected basic characteristics including the type of product (small molecule, biological, or advanced therapeutic medicinal product (ATMP)), pharmacotherapeutic group, indication, accelerated assessment, orphan designation, proactive CMA application, and unmet medical need. The state of the specific obligations was defined at baseline and tracked during each follow-up moment, leading to categorization as specific obligation maintained (no changes made in the specific obligation), change in due date, change in description and change in description and due date, newly imposed specific obligation. The changes were divided into those with minor or major impact on specific obligations. We also assessed whether changes were due to new data submission and if the benefit-risk remained positive after fulfilling or not fulfilling a specific obligation. We monitored specific obligations until they were fulfilled, CMA was withdrawn or revoked, or the end of the study period (30 November 2022). Additionally, we checked in annual renewal reports if initial uncertainties were resolved during the annual renewals.

Data collection

Information about the conditionally authorized products, such as whether the applicant applied for a CMA proactively and the uncertainties that led to the imposition of specific obligations, was obtained from European Public Assessment Reports (EPARs). The uncertainties were identified from the benefit/risk section of the EPARs. The description and due dates of specific obligations, the benefit/risk balance, and information about the fulfilment of specific obligations over time were extracted from confidential CMA annual renewal assessment reports and Type II variation assessment reports, which were accessed through the internal documentation system of the Dutch Medicines Evaluation Board.

Data analysis

We conducted a descriptive analysis to examine the time required to convert a CMA to a standard marketing authorization. Additionally, we performed an exploratory analysis to determine if specific obligations requiring a longer period to be fulfilled or those with major changes had distinct features, such as a CMA application that was not requested proactively. Studies have reported that the median duration for anticancer medicinal products to covert to standard marketing authorization is four years.(10)(7)[9] As we also included products that were approved after 2018, these products were not given sufficient time to be converted due to the short duration of follow-up.

Results

Cohort characteristics

Between 2006 and 2021, 1.128 medicinal products were granted a marketing authorization by the EMA, of which 72 were conditional and thus subject to specific obligation. Of the 72 conditionally approved product, 40 (56%) were anticancer medicinal products.
The 40 included medicinal products were conditionally authorized for 45 initial (hemato-)oncological indications. The most common indications for these products were non-small cell lung cancer (NSCLC), multiple myeloma (MM), gastrointestinal stromal tumors (GIST), diffuse large B cell lymphoma (DLBCL) and breast cancer. Table 1 presents an overview of the characteristics of the medicinal products that were included in the study. We identified 90 specific obligations with a median of 3 specific obligations per medicinal product.

Table 1. Characteristics of anticancer medicinal products granted a CMA (n=40)

Characteristics		
Type of medicinal product (N= 40 medicinal products)		
Small molecule	23	58%
Biological	15	38%
ATMP	2	5%
Pharmacotherapeutic group		
Cytotoxic antibiotics	1	2%
Monoclonal antibodies and antibody drug conjugates	13	32%
CD38 inhibitors	1	2%
EGFR inhibitors	1	2%
PD-1/PDL-1 inhibitors	3	7%
Other monoclonal antibodies and antibody drug conjugates	8	20%
Protein kinase inhibitors	18	44%
ALK inhibitors	4	10%
BCR-ABL tyrosine kinase inhibitors	1	2%
EGFR tyrosine kinase inhibitors	1	2%
HER2 tyrosine kinase inhibitors	2	5%
FGFR tyrosine kinase inhibitors	1	2%
Other protein kinase inhibitors	9	22%
Other antineoplastic agents	9	22%
Indications		
Non-small cell lung cancer (NSCLC)	7	16%
Multiple Myeloma (MM)	6	13%
Gastrointestinal stromal tumors (GIST)	2	4%
Diffuse large B cell lymphoma (DLBCL)	2	4%
Breast cancer	2	4%
Other type of cancer	26	74%
Accelerated Assessment		
Yes	5	13%
No	35	87%
Orphan designation at approval		
Yes	19	48%
No	21	52%
Unmet medical need		
No satisfactory treatment authorized	18	45%
Major therapeutic advantage	22	55%

Proactive request for CMA		
Yes	22	55%
No	18	45%

ATMP, advanced therapeutic medicinal product; CMA, conditional marketing authorization; [a] Based-on ATC code.

Changes in specific obligations

Specific obligations were followed for a median of 2.5 years (IQR 1.6-4.4) with the longest follow-up time being 10.7 years for Caprelsa. During follow-up, 245 states were determined from annual renewal assessment reports and variation type II reports. These variation type II reports contained changes to SOBs, extension of the indication and/or submission of data. Alle determined states of the SOBs are listed in *Figure 1.*

Each year during the renewal process, substantial data was either submitted that had an impact on the SOB or no data was submitted that affected the SOB. In the majority of time no substantial new data was provided that impacted the specific obligations during a renewal. As a result, the SOB either remained unchanged or underwent changes, such as changes to the due date or changes in description, with the majority of description changes being minor, for example altering the wording from "conduct the study" to "submit the study" for the SOB of Arzerra.
When substantial data that impacted a specific obligation was submitted, the obligation could be partially fulfilled if it consisted of multiple elements that needed to be submitted (e.g. an interim report and a final study report or reports of two separate studies). If the specific obligation is not fully or partially fulfilled after the submission of substantial data, it goes through the same process as mentioned for obligations with no substantial data submitted, with one exception in the case of Lartruvo. Upon fulfilling all specific obligations for Lartruvo, no benefit was found in using Lartruvo in combination with doxorubicin versus doxorubicin alone. This resulted in a negative benefit-risk balance for the entire population, leading to the revocation of its conditional marketing authorization. When imposed data are submitted and the specific obligation is fulfilled, the benefit-risk balance is re-evaluated. A positive benefit-risk balance can lead to the imposition of new specific obligations, demanding for example more specified data. If there are any remaining uncertainties a specific obligation can be followed-up in an Annex II condition (2/245 states), or other post-marketing measurements. When there are no remaining specific obligations to be fulfilled, the CMA can be converted to a standard marketing authorization. Of the 40 included medicinal product 24 product were converted to a standard marketing authorization before the end of the follow-up time.

During follow-up, 245 states were determined. Of these states, 140 (57%) comprised maintenance of the specific obligation, 28 (11%) a change in due date, 7 (3%) changes in description, 6 (2%) changes in both due date and description and 63 (26%) obligations were fulfilled. . Sixteen anticancer medicinal products had changes in their due date, description or in both, whereas 24 products had no changes in their respective SOBs (SOB maintained).

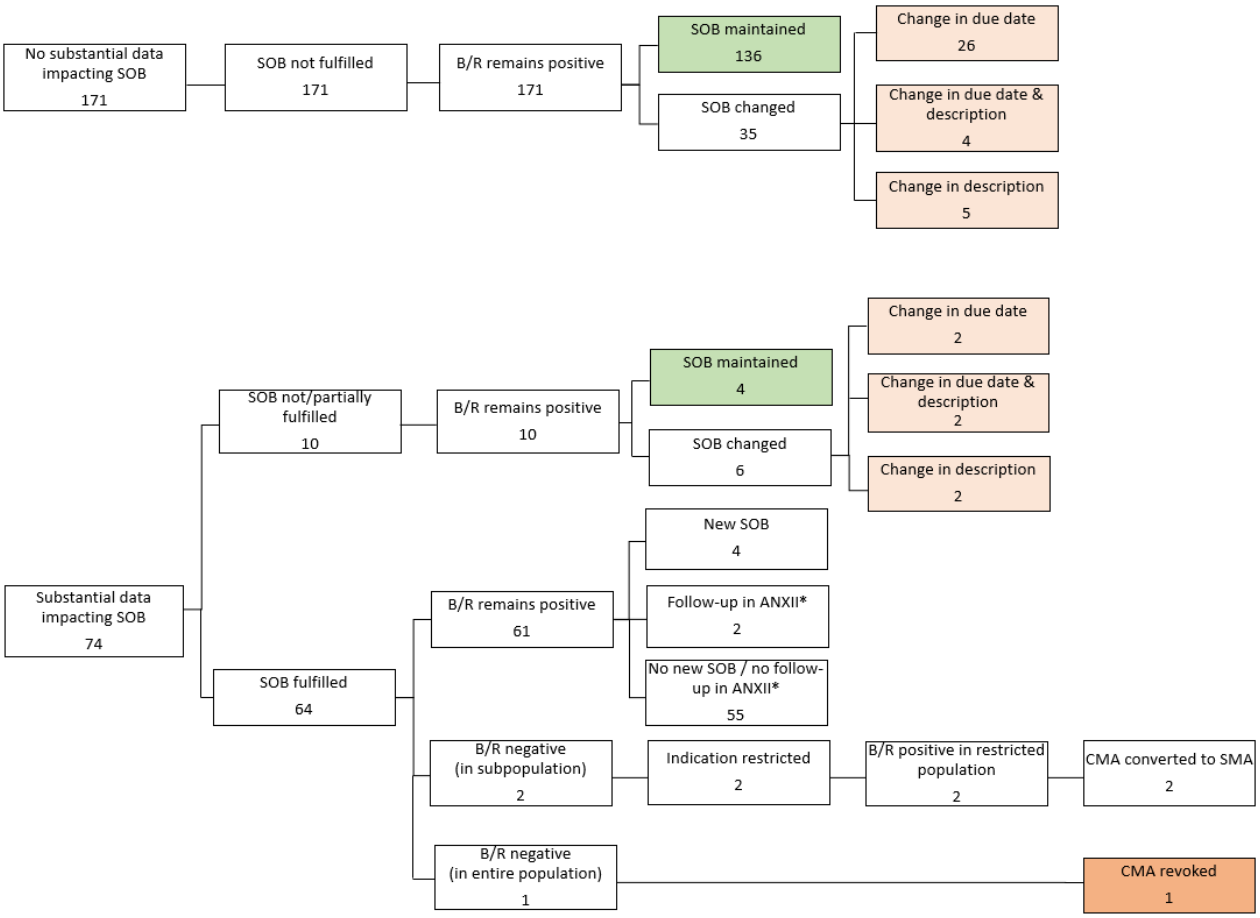

Figure 1 Flowchart visualizing changes made to specific obligation during annual renewals. ANXII, Annex II Condition; B/R, benefit/risk; CMA, conditional marketing authorization; SOB, specific obligation SMA; standard marketing authorization; * The conversion from CMA to SMA occurs when all SOBs are fulfilled. Otherwise, the CMA will be renewed if there are remaining unfulfilled SOBs.

Major changes in description

As previously stated, changes in the descriptions of the SOBs generally resulted in minor changes to the wording. However, there were two instances where the changes led to substantial changes in the SOBs. One such change was in the SOB of Xalkori, where the rapporteurs requested additional safety analysis. Another major change was in the SOB of Tyverb. After the results from the interim analysis of the study that was imposed to fulfill the SOB showed that the study was unlikely to provide significant information, the study was closed prematurely. However, in order to address the remaining uncertainties, the CHMP requested that these uncertainties should be resolved using data from other (ongoing) studies.

Newly imposed SOBs

In four cases, fulfillment of the initial SOBs resulted in the imposition of a new SOB for three medicinal products. The fulfillment of the original SOBs either revealed new uncertainties or failed to resolve existing ones (e.g. Tyverb). Out of these three products, two-thirds (67%) were granted CMA a due to their major therapeutic advantage. These medicinal products with newly imposed SOBs all received a CMA in 2007-2012 and two-thirds (67%) did not proactively apply for a CMA.

Major changes to the marketing authorization

One of the changes that had a major impact on the marketing authorization was that of Rubraca (rucaparib). After the marketing authorization holder submitted substantial data it was concluded that

the benefit/risk of Rubraca in the 'treatment indication' (initially approved indication) was no longer considered favorable while remaining positive in the restricted (extended population). After removing the treatment indication, the restricted indication was no longer subject to any specific obligations and therefore converted to a standard marketing authorization. Another medicinal product for which the indication was restricted after which the CMA was converted into a standard marketing authorization was Caprelsa (vandetanib). During the 7th annual renewal there was a major change in description of the only specific obligation imposed for Caprelsa, after finding that the benefit/risk balance of Caprelsa remained positive in the overall population of the indication, while the benefit/risk balance was negative in the subpopulation (RET negative patients), the indication got restricted to RET positive patients during the 11th annual renewal, in order to convert the conditional marketing authorization into a standard marketing authorization.

Change in due date

During the follow-up period, due dates of 25 specific obligations (28% of all specific obligations) were changed 35 times. Out of these 25 specific obligations, 10 underwent two changes in due date. The total delay in the due date is documented in *Table 2*. The median delay in the due date was 1.8 years, with the longest delay being 6.5 years for Pixuvri, for a SOB that was initially expected to be submitted in 6.9 years. Of these 25 due date changes, nine (67%) resulted in a delay of 3 years or more for specific obligations of medicinal products that were granted a CMA between 2006-2012. The remaining 33% were granted a CMA between 2013-2016. Since 2016, there have been no changes to the due dates that resulted in a total delay of 3 years or more (it should be noted that the latest approved medicinal products in this cohort have had a relatively shorter follow-up period). For 15 changes in due dates, the reason for delay was identified as enrollment delays, including slow patient enrollment and low event rates. In one instance, the reason was commercial unavailability.

Table 2 Change in due date

Total delay in due date (median 1.8 years)	**Number of specific obligations with changed due date (n=25)**
<1 year	7
1 – 2 years	9
≥3 years	9

Follow-up period

Figure 3 displays the duration of follow-up for the included medicinal products. Products that were converted to a standard marketing authorization prior to November 2022 were followed until their conversion date, while products that failed to convert within that time frame were followed until the end of follow-up (November 2022) or the withdrawal of their marketing authorization. Comparing the medicinal products approved between 2006-2012 and those granted conditional marketing authorization between 2013-2018, the median unconverted time/duration of a CMA for the first six years was 5.9 years (IQR 3.8-7.7) and for the latter, it was 2.7 years (IQR 2.0-5.2). This implies that the conversion time of anticancer medicinal products to a regular marketing authorization has decreased over time since the implementation of conditional marketing authorizations by the EMA. Medicinal products with a CMA that have remained unconverted for four years or longer (n=12), in 75% (9 products) applied for a full marketing authorization and did not proactively apply for a conditional marketing authorization.

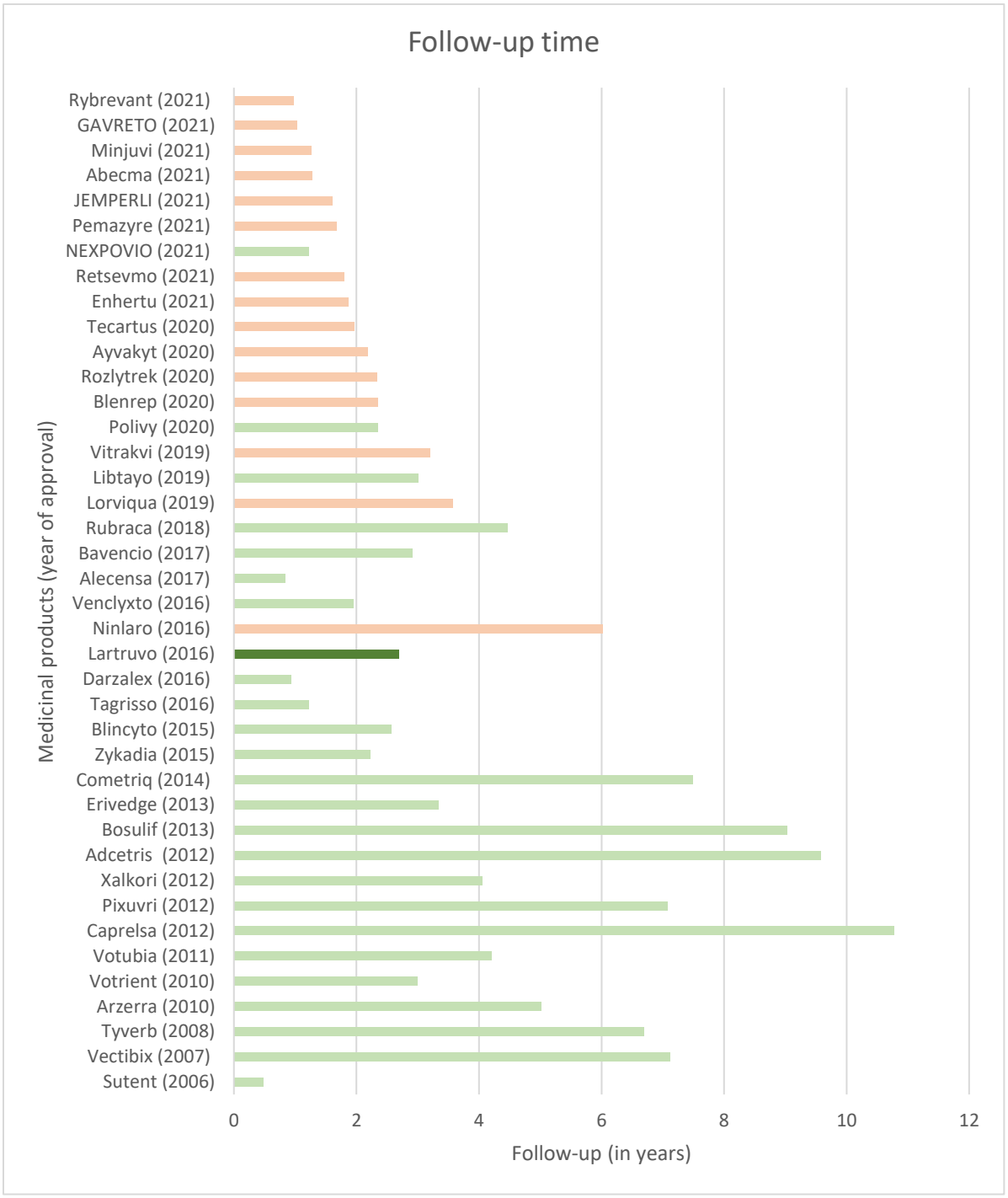

Figure 3. Follow-up period of anticancer medicinal products granted a conditional marketing authorization (CMA). Green= CMA converted to a standard marketing authorization, dark green= CMA revoked, orange= CMA not converted before December 2022.

Discussion:

The aim of this study was to investigate the follow-up of specific obligations required for anticancer medicinal products granted a CMA, including their duration, potential changes, and reasons for these changes. During follow-up, 245 states were determined. Of these, 140 (57%) comprised maintenance of the specific obligation, 28 (11%) change in due date, 7 (3%) changes in description, 6 (2%) changes in both due date and description and 64 (26%) obligations were fulfilled. Changes in description mainly resulted in minor changes to the SOB. However, for two specific products, Xalkori and Tyverb, major changes were made to the SOB. The change in the SOB for Xalkori led to the imposition of a new SOB due to the rapporteurs requesting more detailed information. For Tyverb, the initially imposed SOB was insufficient in providing data and a new SOB was imposed, requesting data from other studies.

Changes in due date:

When a medicinal product is granted a CMA, uncertainties must be resolved post-authorization through specific obligations. The longer it takes for a marketing authorization holder to solve these uncertainties, the longer a patient may be exposed to unknown risks.(10)(7)[10,11]

Nine specific obligations with a delay of 3 years or more were found within this cohort. These changes were found in seven anti-cancer medicinal products, of which five (71%) were granted a CMA between 2006-2012 and two (29%) in 2013 and 2016. After 2016 there were no change in specific obligation that delayed the due date for 3 years or more. Of these seven products, six (86%) did not proactively apply for a CMA. We found that changes in due date are mainly caused by enrollment delay, which is a common problem in pre-authorization cancer clinical trials and may be an even greater problem post-authorization such as observed in our study.[12] One potential reason for the enrollment delay is that, once a product has been conditionally authorized and is on the market, patients and physicians may be less likely to participate in studies, as they may feel less motivated, given that the product is already available.

To enhance the rate of timely completion of SOBs and provide complete evidence packages for drugs approved by EMA , it is important for regulators to enforce compliance of SOBs within an excepted timeframe. This is crucial in ensuring public health and availability of high-quality, safe and effective medicines. Companies can be motivated to complete SOBS in a timely manner by making the status reports and results of such studies publicly accessible. Although there is a database in the United States, the EU did not follow this example yet.(11)[13] Another suggestion made to avoid delays in specific obligations, is to only include studies that are initiated pre-approval and have a well-underway recruitment process.(12)[14]

Changes in marketing authorization

Besides changes in due dates and wording, two major changes were made to the indication of the CMA. One of these changes were made for Caprelsa. A major change to the indication was made after seven annual renewals, leading to a restriction on the target population due to insufficient data. This change led to the fulfillment of the specific obligation. Similarly, Rubraca also experienced a change in indication. The initial indication got restricted after extension of the indication. It took 10.7 years for the CMA of Caprelsa to be converted to a standard marketing authorization. We should question whether this change could have been anticipated earlier as no substantial data was submitted after seven years, potentially exposing patients to unknown risks. This also applies to other medicinal products with a long conversion time and/or long delays in due date. Although in the majority of the identified states the specific obligations were fulfilled as imposed, we should consider whether it is acceptable for a product to remain on the market for such a long time when uncertainties persist. For

example, the uncertainties for the restricted populations of Caprelsa and Rubra are not resolved. Although only two out of 40 (5%) products were impacted, we need to decide if these are exceptional cases or if intervention is necessary when similar situations arise in the future.

Change in time to conversion

Our results show that there has been a reduction in the time needed to convert a CMA into a standard marketing authorization when comparing the first six years of the implementation of CMAs (median of 5.9 years in 2006-2012) to the subsequent six years (median of 2.7 years in 2013-2018). This suggests that the conversion time for anticancer medicinal products to a standard marketing authorization has decreased over time, thereby reducing the time patients are exposed to unknown effects. This may also be due to more proactive applications seeking a CMA at submission. In the first ten years of CMA implementation, the number of applicants proactively seeking a CMA increased overtime.(8)[15] Our study also reflects this, between 2006 and 2012 30% (3/10) of the anticancer medicinal products received a CMA after proactive application, rising to 54% (7/13) in 2013-2018. From 2019 to 2021, 71% (12/17) of the products were granted a CMA after proactive application. Our study also found that 75% of products with a CMA that were not converted to a standard marketing authorization within 4 years, did not proactively apply for a CMA at submission. Within recent years, more applicants seeking a CMA at submission, this may lead to a shorter unconverted period. This corresponds with a recent study suggesting that marketing authorization holders have improved their use of CMAs overtime as a regulatory tool, through better planning and proactive interaction.(13)

Limitations:

In this study, we analyzed anticancer medicinal products that were granted a conditional marketing authorization (CMA) between 2006 and 2021. Therefore, for more recently authorized medicinal product, only limited follow-up was possible. Previous research has shown that the median time for a CMA to be converted to a standard marketing authorization is four years. To account for this, we compared products with at least four years of follow-up (until 2018), since products approved after 2018 were less likely to be converted within the limited follow-up period.

We were also unable to determine if the initial uncertainties that led to specific obligations (SOBs) were resolved when an SOB was fulfilled. This information was not reported in most of the annual renewal assessment reports and type II variation reports. We suggest that this information should be noted in future assessment reports to ensure transparency and determine if all uncertainties are resolved when a SOB is fulfilled/CMA is converted to a standard marketing authorization.

In conclusion, despite changes occurring in specific obligations, overall, most of time specific obligations are fulfilled as imposed and within the initially imposed due date. Especially in later years, only few major delays in due date (delay three years or more)/and or description occurred. Also, the time for a CMA to be converted to a standard marketing authorization decreased over time .This suggests that the current systems and procedures in place for managing conditional marketing authorizations are effective in ensuring the ongoing safety and efficacy of these products and may have been become better overtime.

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