Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study

Lourens T. Bloem[1,2], Aukje K. Mantel-Teeuwisse[1], Hubert G. M. Leufkens[1], Marie L. De Bruin[1,3], Olaf H. Klungel[1,4] and Jarno Hoekman[5]

When medicines are granted a Conditional Marketing Authorisation (CMA) in Europe, specific obligations are requested to obtain comprehensive data on benefits and risks. We performed a retrospective cohort study to characterize obligations, examine changes to their description and due dates after initial authorization, determine timing of data submission relative to due dates, and identify drug-related, procedure-related, and obligation-related factors associated with change. We identified 69 obligations for 26 medicines conditionally authorized between 2006 and 2016. We found 39 changes to 27 obligations (39% of obligations), of which four substantially changed the obligation. For 55% of obligations, data submission was delayed. Eleven factors were associated with change, including the use of CMA as a rescue option. The results are potentially indicative of a continuous search by regulators to reduce uncertainties. Submission delays impact public health negatively by prolonging exposure of patients to unknown risks, particularly when the level of uncertainty is high.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Specific obligations to resolve uncertainties for conditionally authorized medicines in Europe are not always completed in time and knowledge gaps may not be filled.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated changes made to obligations after initial authorization, whether drug-related, procedure-related, and obligation-related factors were associated with change, and timing of data submission relative to due dates.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ At least one change, mostly to the due date, was made to 39% of obligations. Four substantially changed the design of the study. Eleven factors were associated with change to obligations that can be instrumental in facilitating regulatory learning about uncertainties of conditionally authorized medicines.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Regulatory learning about benefits and risks of conditionally approved medicines is facilitated by prospective planning of obligations and when additional attention is paid to obligations addressing a high level of uncertainty.

One of the major challenges for contemporary medicines marketing authorization (MA) is to provide timely access to medicines while ensuring that remaining uncertainties about the benefit-risk profile are adequately addressed. To resolve uncertainties, data need to become available postauthorization, often as part of requests for postmarketing studies by regulators. However, whether these studies are actually conducted, whether this happens in an acceptable and agreed-upon timeframe, and, ultimately, whether uncertainties are indeed resolved is subject to debate in several jurisdictions.[1–13] Recently, we and others found that studies are not completed in time[8,10–12] and knowledge gaps are not filled,[7,9–11] whereas the conduct of additional studies is not enforced and regulatory decisions are not revised.[7,11] These observations led to a call for stricter regulatory action to protect patients.[7–10,12]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Dutch Medicines Evaluation Board, Utrecht, The Netherlands; [3]Copenhagen Centre for Regulatory Science, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [5]Innovation Studies, Copernicus Institute of Sustainable Development, Utrecht University, Utrecht, The Netherlands. Correspondence: Jarno Hoekman (j.hoekman@uu.nl)

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Postauthorization studies are particularly important for authorization pathways that aim to provide timely access to medicines that address an unmet medical need, such as the United States Accelerated Approval program, Canada's Notice of Compliance with Conditions policy, and the European Union (EU) Conditional Marketing Authorization (CMA). In general, for these pathways, less conclusive data on benefits and risks, and, therefore, a higher degree of uncertainty, is accepted as compared to standard authorization pathways. Uncertainties may follow from: a lower number of patients studied prior to authorization; shorter duration of follow-up; the (single-arm) design of pivotal studies; or the use of a surrogate end point rather than a clinical end point. These uncertainties are accepted by regulators, provided that drug developers commit to the provision of additional data postauthorization.

In the case of the EU CMA pathway, imposed mandatory postauthorization studies are called specific obligations. They are imposed in addition to tools used to identify and characterize uncertainties in all EU marketing authorization pathways, such as the Risk Management Plan and Periodic Safety Update Reports. To keep track of the progress and results of obligations, the CMA is subject to an annual renewal process instead of the conventional 5-year renewal. During annual renewal, the benefit-risk balance of the medicine is re-assessed together with an assessment of the progress and results (when available) of ongoing and completed obligations. An in-depth description of this process is provided in **Box S1**.

Previous research flagged concerns about the progress and results of postauthorization studies in the context of the CMA pathway.[6,8,9] These studies created awareness of possible concerns about compliance, but there are still several unanswered questions about the commitments to conduct specific obligations in the postauthorization phase. First, we know little about the process of annual renewals and the fate of obligations over time. A previous study by the European Medicines Agency (EMA) revealed that changes were made to obligations after initial authorization and concluded that this only concerned few obligations and mainly nonmajor changes.[14] This study did, however, neither follow obligations over time nor examine the type of obligations that were changed or delayed. Second, we lack data on whether there are any factors associated with changes to obligations. Knowledge about such factors can be instrumental for regulators to identify the best way to learn about a medicine's benefit-risk profile and resolve remaining uncertainties within a reasonable timeframe. Therefore, the aim of the present study is to characterize changes made to obligations over time, determine timing of data submission, and identify drug-related, procedure-related, and obligation-related factors associated with change.

RESULTS

Cohort description

Between March 29, 2006, and December 31, 2016, 35 medicines were granted a CMA. Of these, three vaccines and six medicines with either <1 year of follow-up or lack of a renewal before the end of the study period were excluded. Of the remaining 26 medicines (characteristics provided in **Table S1**), no CMAs were revoked by the EMA or withdrawn by the company and 50% of the CMAs were converted to a standard MA during the study period. We included all 69 specific obligations for these 26 medicines (median 2 per medicine, interquartile range (IQR) 1–2; **Table 1**). Of these, two obligations were imposed after a medicine was approved, both for panitumumab. Almost 75% of the obligations ($n = 51$) had been removed by the end of follow-up. In 22 cases, this coincided with the conversion of the CMA into a standard MA. The vast majority ($n = 48$) were removed because they were considered fulfilled, except for three obligations for darunavir. These were downgraded to postauthorization studies that, although mandatory, were no longer a condition for maintaining the CMA, because the requested data were already available or no longer considered relevant. The process of identification of the obligations is shown in a flowchart in **Figure 2**.

Changes to specific obligations

During follow-up (median 2 renewals including conversions, IQR 1–4), we identified 39 changes in 27 obligations (39% of all obligations). Changes involved a change in due date ($n = 17$; 44%), which were all extended; a change in (text) description ($n = 5$; 13%; as explained in **Box S1**); or a change in description and due date ($n = 17$, 44%), of which all but two were extended. Of 27 changed obligations, 19 were changed once, 5 were changed twice, 2 were changed thrice, and 1 was changed four times. The median time-to-first-change was two renewals (IQR 1–2; actual time 673 days, IQR 385–833). All obligations and the changes made to them are visually depicted in **Figure 1**, which shows a "heat map" of changed obligations, ranging from most (often) changed to least changed.

Further analysis showed that most description changes had either a negligible ($n = 10/22$) or minor impact ($n = 8/22$) on the initially requested activity. The remaining four description changes had a major impact. They affected four different obligations of four different medicines. An overview of the description changes, the assessment of impact, and reasons for change is provided in **Table S2**. Additionally, the process of identification of the obligations and changes is shown in a flowchart in **Figure 2**.

All four obligation changes assessed as having major impact were imposed between 2007 and 2012 for small molecule medicines (crizotinib, etravirine, lapatinib, and stiripentol) for which alternatives were available. All obligations addressed a clinical uncertainty identified at time of MA. The initially requested activity concerned an interventional phase III study, which in three out of four needed to be initiated after authorization. With regard to changes, two studies were downgraded from an initially requested randomized clinical trial to a retrospective observational study, one study was discontinued and replaced by data from three ongoing studies and for one study an additional detailed safety analysis was requested following an assessment of interim results.

Timing of data submission

Because the data submission date was not available for one obligation, we assessed the timing of data submission for 47 obligations that were removed because they were considered fulfilled. The timeframe to data submission as initially set by the EMA was on median 394 days (IQR 159–759 days). Data were submitted on median 2 days after the initial due date (IQR −25 to +125 days). Overall, for 55% ($n = 26/47$) of the obligations, data were submitted after the initial due date, with 23% ($n = 11/47$) submitted

Table 1 Characteristics of obligations (*n* = 69) and assessment of associations between drug-related, procedure-related, and obligation-related factors and change to specific obligations

Factor	No change *n* = 42 (%)	Change *n* = 27 (%)	RR[a]	95% CI
Drug-related				
Marketing authorization applicant size				
Big pharma	39 (61)	25 (39)	Ref.	N/A
Small and medium-sized enterprises	3 (60)	2 (40)	1.0	0.33–3.1
Drug type				
Small molecule	30 (67)	15 (33)	Ref.	N/A
Biological/ATMP	12 (50)	12 (50)	**1.5**	**0.84–2.7**
Indication				
Infectious disease	15 (68)	7 (32)	Ref.	N/A
Oncology	24 (57)	18 (43)	1.3	0.67–2.7
Other	3 (60)	2 (40)	1.3	0.37–4.3
FDA approval				
Regular approval	8 (53)	7 (47)	Ref.	N/A
Accelerated approval	29 (62)	18 (38)	0.82	0.43–1.6
No approval	5 (71)	2 (29)	**0.61**	**0.17–2.2**
Size of studies delivering main/pivotal evidence at MAA				
0–500 patients	25 (57)	19 (43)	Ref.	N/A
>500 patients	17 (68)	8 (32)	0.74	0.38–1.4
Procedure-related				
Prospective use of CMA pathway				
No	23 (53)	20 (47)	Ref.	N/A
Yes	19 (73)	7 (27)	**0.58**	**0.28–1.2**
CHMP experience with CMA pathway				
Imposed in 2006–2008	21 (68)	10 (32)	Ref.	N/A
Imposed in 2009–2016	21 (55)	17 (45)	1.4	0.75–2.6
Accelerated assessment during the MA procedure				
No	39 (60)	26 (40)	Ref.	N/A
Yes	3 (75)	1 (25)	**0.63**	**0.11–3.5**
Re-examination during MA procedure				
No	27 (61)	17 (39)	Ref.	N/A
Yes	15 (60)	10 (40)	1.0	0.56–1.9
SA/PA received before authorization				
No	17 (61)	11 (39)	Ref.	N/A
Yes	25 (61)	16 (39)	0.99	0.55–1.8
Adherence to SA/PA				
No	13 (68)	6 (32)	Ref.	N/A
Yes	10 (53)	9 (47)	**1.5**	**0.66–3.4**
No advice provided	19 (61)	12 (39)	1.2	0.55–2.7
Scope of Commission Regulation (EC) No. 507/2006 – Orphan designation				
No	27 (60)	18 (40)	Ref.	N/A
Yes	15 (63)	9 (38)	0.94	0.50–1.8
Scope of Commission Regulation (EC) No. 507/2006 – Treatment for seriously debilitating or life-threatening disease				
No	6 (67)	3 (33)	Ref.	N/A
Yes	36 (60)	24 (40)	1.2	0.45–3.2

(Continues)

Table 1 (Continued)

Factor	No change *n* = 42 (%)	Change *n* = 27 (%)	RR[a]	95% CI
Argumentation for unmet medical need				
No satisfactory method of diagnosis, prevention or treatment authorized	10 (63)	6 (38)	Ref.	N/A
Other	32 (60)	21 (40)	1.1	0.52–2.2
CHMP agreement on MA				
Consensus	25 (68)	12 (32)	Ref.	N/A
Majority	17 (53)	15 (47)	1.4	0.80–2.6
MA procedure active time				
≤200 days	5 (56)	4 (44)	Ref.	N/A
201–210 days	21 (64)	12 (36)	0.82	0.35–1.9
>210 days	16 (59)	11 (41)	0.92	0.39–2.2
MA procedure clock-stop time				
≤160 days	22 (69)	10 (31)	Ref.	N/A
>160 days	20 (54)	17 (46)	**1.5**	**0.79–2.7**
MA procedure calendar time				
≤1 year	19 (73)	7 (27)	Ref.	N/A
>1 year	23 (53)	20 (47)	**1.7**	**0.85–3.5**
Obligation-related				
Addressed uncertainty				
Clinical effect	34 (58)	25 (42)	Ref.	N/A
Other	8 (80)	2 (20)	**0.47**	**0.13–1.7**
Study status				
Ongoing study	29 (71)	12 (29)	Ref.	N/A
New study	7 (39)	11 (61)	**2.1**	**1.1–3.8**
Other obligation (no study)	6 (60)	4 (40)	1.4	0.56–3.3
Study design				
Interventional	35 (63)	21 (38)	Ref.	N/A
Observational	1 (33)	2 (67)	**1.8**	**0.75–4.2**
Other obligation (no study)	6 (60)	4 (40)	1.1	0.46–2.4
Development phase addressed by obligation				
Late clinical (phase III)	18 (51)	17 (49)	Ref.	N/A
Early clinical	13 (87)	2 (13)	**0.27**	**0.072–1.0**
Postclinical	11 (58)	8 (42)	0.87	0.46–1.6

ATMP, advanced therapeutic medicinal product; CHMP, Committee for Medicinal Products for Human Use; CI, confidence interval; CMA, conditional marketing authorization; EC, European Commission; FDA, US Food and Drug Administration; MA, marketing authorization; MAA, marketing authorization application; N/A, not applicable; PA, protocol assistance; RR, risk ratio; SA, scientific advice.
[a]Associations based on disproportionality in bold.

more than half a year later. Strikingly, the three obligations with the longest time to data submission (5–6 years) all underwent changes that had a major impact on the initially requested activity. For all changed obligations, the timing of data submission is depicted in **Figure 1**.

Of the 47 obligations, for 18 obligations the initial due date was adjusted at least once. When including these updated due dates in the analysis, data were submitted on median 14 days before the updated due date (IQR −73 to −1 days). For 23% ($n = 11/47$) of the obligations data were submitted after the updated due date. For nine of these obligations this happened within 2 weeks and for two obligations after 92 and 292 days, respectively (both for panitumumab).

Factors associated with change to obligations

For all 69 obligations we further explored potential factors for change by calculating risk ratios (RRs; **Table 1**). Based on our chosen cutoff points, we identified 11 drug-related, procedure-related, and obligation-related factors that were associated with change to obligations. The drug-related factors associated with change were drug type (biological or advanced therapeutic medicinal product (ATMP) vs. small molecule; 50% vs. 33% changed;

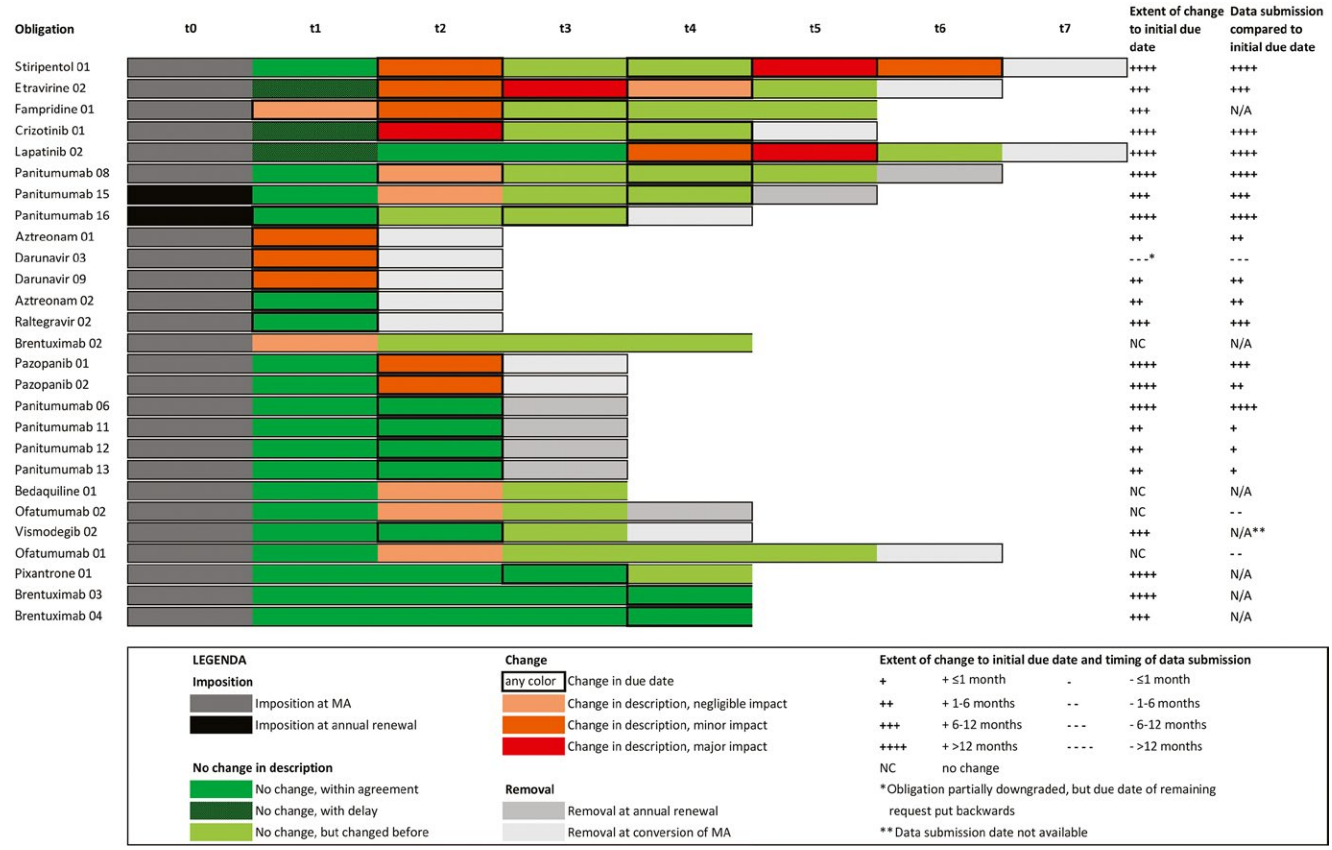

Figure 1 Visualization of changes made to specific obligations and overview of timing of data submission for all changed obligations (n = 27). Ordered to number of changes, timing of change, type of change and time at risk of change; further listed by alphabet. MA, marketing authorization; N/A, not applicable.

RR = 1.5) and US Food and Drug Administration (FDA) approval (no approval vs. regular approval; 29% vs. 47% changed; RR = 0.61). The procedure-related factors associated with change were prospective use of CMA pathway (yes vs. no; 27% vs. 47% changed; RR = 0.58), accelerated assessment during the MA procedure (yes vs. no; 25% vs. 40% changed; RR = 0.63), adherence to scientific advice or protocol assistance (yes vs. no; 47% vs. 32% changed; RR = 1.5), MA procedure clock-stop time (i.e., the portion of the approval process during which the company prepares answers to questions posed by regulators (>160 days vs. ≤160 days; 46% vs. 31% changed; RR = 1.5) and MA procedure calendar time (i.e., the full length of the approval process including time for re-examination, where applicable; >1 year vs. ≤1 year; 47% vs. 27% changed; RR = 1.7). The obligation-related factors associated with change were addressed uncertainty (other vs. clinical effect; 20% vs. 42% changed; RR = 0.47), study status (new study vs. ongoing study; 61% vs. 29% changed; RR = 2.1), study design (observational vs. interventional; 67% vs. 38% changed; RR = 1.8), and development phase addressed by obligation (early clinical vs. late clinical; 13% vs. 49% changed; RR = 0.27).

DISCUSSION

The aim of this study was to characterize specific obligations imposed on the CMA of medicines licensed by the EMA, examine changes to their description and due dates after initial authorization, determine timing of data submission relative to due dates, and drug-related, procedure-related, and obligation-related factors associated with change. The results indicate that a relatively large proportion of obligations (27/69; 39%) was changed at least once between their imposition and removal or the end of follow-up. The majority of these changes concerned at least a change in due date (34/39) necessary to account for delays. In line with previous research,[6,8] we found that for 11 obligations, data were submitted more than half a year later, reflecting substantial delays in data availability. Additionally, four changes to the description of obligations had a major impact on the initially requested activities, severely affecting the data that would become available.

Various studies have interpreted results like our study by focusing on whether companies indeed honor postmarketing commitments,[1–5,7,10–12] with three of these studies focusing specifically on the CMA pathway.[6,8,9] Our study contributes to the findings of these studies by demonstrating that the majority of obligations attached to CMAs are honored. Our results also suggest that regulators make extensive use of the annual renewal procedure to assess the progress of obligations. This is evident from the observation that, in most cases, regulators make small changes to obligation descriptions that do not have a major impact on the initially requested activity. However, we also show that due date changes do result in considerable delays in

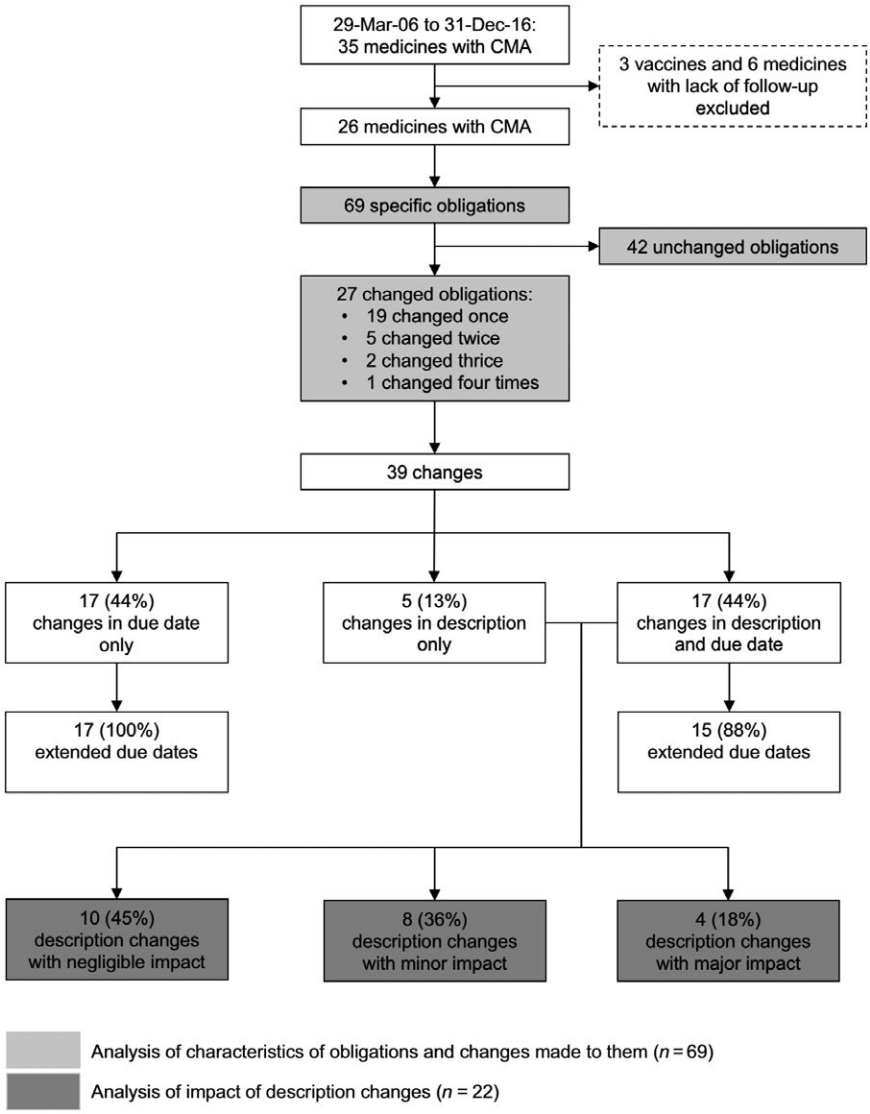

Figure 2 Flowchart showing the process of identification of obligations and changes. CMA, conditional marketing authorization.

data availability. The consequences for public health of these delays might be substantial. Because these are medicines for which relatively many uncertainties exist, patients may unnecessarily be exposed to unknown risks, especially when their physician is unable to accurately assess the impact of these uncertainties.[15] The results show that these risks could have been characterized earlier if initial due dates were adhered to. A previous study by Davis *et al.*[16] also showed that for most oncology medicines authorized based on limited evidence regarding benefits, evidence on overall survival and quality of life was still not available after a minimum of 3.3 years after authorization. This suggests that accepted uncertainties at the time of authorization may not readily be resolved, making it difficult for physicians, patients, and other stakeholders to make informed decisions without knowledge of the added clinical value of a medicine. These findings underline that regulators should be reluctant to accept changes and additional delays, unless strictly necessary to yield relevant results.

Given that we conducted a process study that followed obligations over time, our study can also provide insights in regulatory learning, which is of great importance for the CMA pathway in order to further characterize the benefit-risk profile of a medicine through regulatory interventions (specific obligations). The observed changes to obligations mostly involved alterations of details of the obligations and thereby may represent a continuous regulatory search for the right way to receive desired information while adapting to unforeseen situations along the way. Indeed, in response to other research,[12] regulators have mentioned that changes to postauthorization studies may be necessary to adjust to, for example, advances in science or changes in clinical practice.[13] In the end, regulators are limited in foreseeing outcomes and possible issues encountered along the way. Of note, changes to obligations do not decrease over time, suggesting that adaptations during annual renewal have become an important way for regulators to steer what data becomes available in the postmarketing phase.

However, the shift of a large body of evidence generation from the pre-authorization to the postauthorization phase puts pressure on regulators to make the process of conducting obligations

as efficient and effective as possible in order to ensure that comprehensive data are available in a timely manner. Our study may assist in this challenge as it identified 11 factors disproportionally associated with change to obligations. These factors point toward two major conditions under which learning about a medicine's uncertainties in the postauthorization phase can be more or less effective and efficient. Although these analyses had limited statistical power, we did observe a few patterns that support insights from previous research. First, prospectively planning a CMA following early dialogue and along with timely consideration of relevant and feasible obligations seems to contribute to receiving additional data in time, as suggested before.[8,17] We found that this approach also results in less need to change the request along the way. This is demonstrated by a relatively small number of changes associated with: (i) an applicant's request for CMA at time of application for a MA as compared to using the CMA as a "rescue option" later in the procedure; (ii) imposition of ongoing studies as a specific obligation (by regulators) as compared to imposition of new studies; (iii) an accelerated assessment of the application; and (iv) and (v) longer review times both in terms of the answering of outstanding questions from regulators by companies and the entire duration of the approval process, also including review time by regulators. Accelerated assessment can be granted following an early request for consideration of this approach and, additionally, applicants are urged to request a presubmission meeting during which they can already present the data and Risk Management Plan that supports the application,[18] thereby necessitating prospective planning. Relatively long review times indicate that uncertainties arising from insufficiently prepared application dossiers necessitate an iterative and reactive process to establish feasibility of the CMA. This requires a considerable amount of time from both the regulators assessing the applications and the applicant providing answers to questions. These observations suggest that use of the CMA pathway should be restricted to those situations in which it is planned prospectively and following early dialogue.

Second, the level of uncertainty about benefits and risks may play an important role, as illustrated by the fact that: (i) obligations addressing a clinical uncertainty as compared to other uncertainties (e.g., pharmacokinetics, monitoring of drug resistance, collecting information on medical practice); (ii) biologicals and ATMPs as compared to small molecule medicines; (iii) late-phase clinical studies (i.e., phase III/confirmatory studies) as compared to early-phase clinical studies; and (iv) new as compared to ongoing studies were all associated with obligation change. Learning under conditions of uncertainties is less straightforward and our study suggests that it is accompanied more often by unforeseen issues. An example is the greater ease of defining and performing exact follow-up activities based on an already ongoing study (possibly even with subject recruitment already finished) as compared to a new study. The four changes in description with a major impact on the initially requested activity also support the view that the level of uncertainty may complicate the learning process: they were all phase III studies that addressed a clinical uncertainty and three were newly initiated. The results suggest that regulators should pay additional attention to obligations that address a high level of uncertainty at MA and continue to do so throughout the drug life-cycle.

The results also raise the question whether a CMA should be granted when the level of uncertainty is substantial. The moment of approval in a drug's life-cycle and the resulting consequences for additional data generation have been a subject of concern, arguing that a window of opportunity for generating data is lost when medicines are authorized early in the life-cycle. First, obtaining comprehensive data postauthorization may be complicated by patients who do not want to participate in requested studies when a medicine is already on the market.[19] This may explain why a large proportion of obligations were delayed. Indeed, a report by the EMA suggest that the main reason for due date changes were recruitment issues and in the case of brentuximab vedotin "the context of an already registered indication" was even explicitly noted as a reason for slow recruitment.[14] Second, companies may be stimulated to perform adequate studies by the prospect of receiving a marketing authorisation.[19] This view is supported by our finding that obligations were less likely to be changed when no FDA approval for the medicine was obtained, as compared to regular FDA approval. This may stimulate companies to conduct these studies thoroughly and as soon as possible, in order to obtain necessary data for FDA approval. Third, the pre-authorization phase offers less complex (i.e., more structured and controlled) conditions for learning. These latter two may be less so postauthorization, resulting in an iterative process of conducting studies through continuous fine-tuning. Regulators should, therefore, carefully consider the moment of (conditional) approval and the impact of the identified uncertainties, bearing in mind that data may become available later than expected.

There are a number of limitations to our study. Although the study cohort was relatively small, we were able to identify multiple factors associated with obligation changes based on disproportionality. However, although our results add substantially to the accumulating research on this topic, we did not answer the question whether submitted data indeed solve the outstanding issues or uncertainties they address and, thus, to what extent the observed delays and changes impacted knowledge about the clinical value of these medicines. This question is of utmost importance for patients and physicians who require confirmation of the benefit-risk profile based on robust data on long-term safety and effectiveness to allow for optimally informed decision making on treatment. Therefore, this is an important focus for future research.

In conclusion, we identified changes in 39% of the obligations imposed as a condition to a CMA, representing several changes with a major impact on the initially requested activities, and partially accounting for a delay in 55% of obligations. Additionally, we identified 11 factors associated with these changes that are potentially indicative of a continuous regulatory search for ways to reduce uncertainties of conditionally authorized medicines. Although the existing regulatory framework seems sufficient to address these issues and, therefore, policy reform may not be needed, efforts to improve implementation of CMA within that framework could be pursued. To facilitate further effective and efficient regulatory learning about benefits and risks of conditionally approved medicines, regulators are advised to ensure that

CMAs are prospectively planned, consider the moment of approval in a medicine's life-cycle, and pay extra attention to obligations that address a high level of uncertainty.

METHODS

Selection and extraction of specific obligations

We performed a retrospective cohort study of specific obligations imposed as a condition to the CMA of medicines licensed since 2006 in the EU (i.e., when the CMA regulation came into use). Eligible medicines were identified by searching EMA annual reports and the EMA website (www.ema.europa.eu). Vaccines were excluded, because they were authorized as mockups, only to be used in emergency situations and with obligations not actively being followed up by the MA holder. Obligations for CMA medicines that were authorized for at least one year or with one annual renewal up to December 31, 2016, were included.

Specific obligations for each conditionally authorized medicine were extracted from lists of obligations provided in Annex IIC to the MA of medicines consisting of a text description and one or more due dates for data submission. We considered each demarcated piece of text in Annex IIC describing one or more postauthorization activities ("the description") with one or more due dates for data submission as a separate obligation. If more than one due date was provided for an obligation, the latest due date was considered the final due date. Included obligations were followed during each annual renewal of the CMA. Follow-up was discontinued after the obligation was removed from Annex IIC at annual renewal, after conversion, withdrawal, revocation, or suspension of the CMA or at the end of the study period, December 31, 2016, whichever came first.

To extract descriptions and due dates of obligations over time, we searched European Commission (EC) decision documents and EMA documentation (Annexes IIC to the MA, minutes, and assessment reports of the Committee for Medicinal Products for Human Use (CHMP)) on the MA granting, annual renewals, and conversion of the selected CMA medicines. EC decisions documents and the Annexes IIC were accessed through the EC Community Register of medicinal products (http://ec.europa.eu/health/documents/community-register/html/index_en.htm). CHMP minutes and assessment reports were accessed through the EMA's internal meeting documentation system. These data were available as part of a Memorandum of Understanding between Utrecht University and the Dutch Medicines Evaluation Board. Dates of inclusion in the Annex IIC were noted, using the corresponding EC decision dates. Extracted data were cross-checked against a recent EMA report.[14] Furthermore, the obligation data submission dates were also extracted from this report.

Characterization of changes to specific obligations

We determined the state of obligations at baseline and for each moment of follow-up. Together, this resulted in a categorization of obligation states in nine mutually exclusive categories describing imposition, no change, change, or removal of the obligation (**Table 2**). The possible states of obligations over time are depicted in **Figure 3**. When an obligation description concerned multiple activities with separate due dates per activity and one or more but not all of these activities and associated due dates were removed, we regarded this as continuation of the obligation rather than a change and categorized it as "no change."

Description changes were further assessed by two researchers (L.B. and J.H.) as having a negligible impact on the initially requested activity (i.e., further specifications of initial obligations), a minor impact (i.e., requests for limited additional or less data, but not expected to severely affect what data will come available), or a major impact (i.e., requests that are expected to severely affect what data will come available). For those changes assessed as having a major impact we read relevant EMA documentation (e.g., European Public Assessment Reports) to provide a narrative of the regulatory decision-making process.

Table 2 Definitions for obligation states used for characterization

Obligation state	Definition
Imposition	
Imposition at MA	Obligation included in the initial Annex IIC to the conditional marketing authorization
Imposition at annual renewal	Newly identified obligation, not previously included in Annex IIC[a]
No change	
No change, within agreement	Obligation description and due date unchanged in Annex IIC[a] and: (a) no data submitted and follow-up date < final due date; or, (b) data submitted since previous follow-up and data submission date ≤ final due date[b]
No change, with delay	Obligation description and due date unchanged in Annex IIC[a] and: (a) no data submitted and follow-up date ≥ final due date; or, (b) data submitted since previous follow-up and data submission date > final due date
Change	
Change in description[c]	Obligation description and/or obligation due date other than the final due date changed in Annex IIC[a]
Change in due date	Final due date of obligation advanced or extended in Annex IIC[a]
Change in description and due date[c]	Obligation description and/or obligation due date other than the final due date changed, plus final due date either advanced or postponed in Annex IIC[a]
Removal	
Removal at annual renewal	Previously included obligation no longer in Annex IIC following annual renewal[a]
Removal at conversion of MA	Previously included obligation no longer in Annex IIC following conversion of MA[a]

MA, marketing authorization.
[a]Annex IIC following annual renewal or conversion compared to the Annex IIC at the last moment of follow-up (i.e., annual renewal or MA). Other procedures were not taken into account.
[b]The due date refers to the data submission. There is a delay between data submission and assessment of the data followed by removal of the obligation from Annex IIC. Therefore, an obligation could be considered to be within the agreed timeline because data was submitted on time while it is maintained in Annex IIC because the data had not yet been assessed.
[c]Changes in obligation description were assessed as having a negligible, minor, or major impact on the initially requested activities.

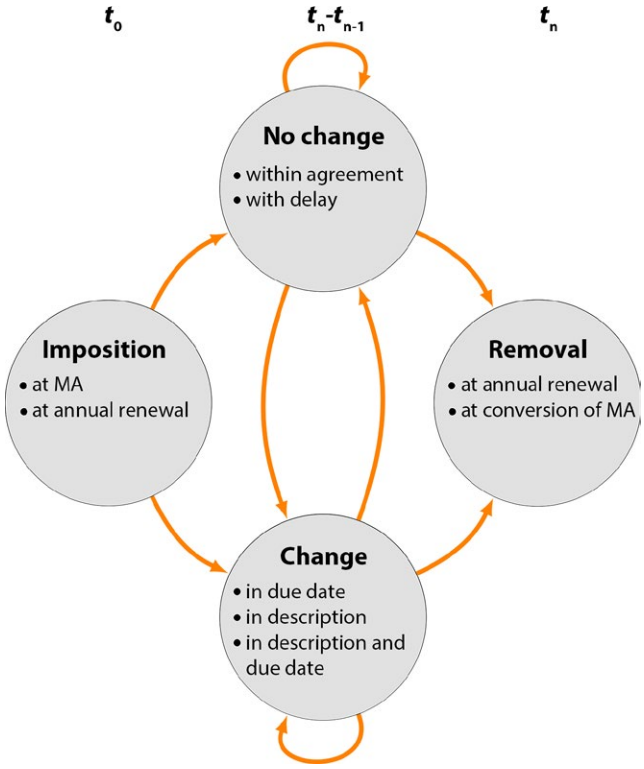

Figure 3 Dynamics in obligation states over time. The arrows indicate changes in obligation states following the assessment of progress and results of obligations during annual renewal. MA, marketing authorization.

Timing of data submission

For each obligation for which data submission resulted in removal of the obligation because they were considered fulfilled, we established the timing of data submission relative to the due date by calculating the difference between the data submission date and both (i) the initially imposed final due date, and (ii) the updated final due date (only in case an adjustment to the initial due date was made). If several changes to the due date had been made, the last change was used.

Potential factors associated with change to specific obligations

We extracted several prespecified drug-related, procedure-related, and obligation-related factors mainly based on previous research on the CMA procedure,[8,17] to assess associations with change to obligations (**Table S3**). For some procedure-related factors, these studies showed that a more complicated procedure was associated with more issues postauthorization.

EC decision documents and EMA documentation were used to extract most data on these factors. FDA documentation was used to extract data on whether the FDA approved the medicines. In addition, data from a recent EMA report[14] was used to cross-check extracted data and to extract the number of patients studied before MA application and data on the provision of and adherence to scientific advice and/or protocol assistance. We included three categorical factors concerning the duration of the MA procedure (i.e., the time between submission of the dossier and the opinion of the CHMP), according to the "types" of time that can be distinguished. The first two factors concern "active time," during which the regulators initially assess the dossier and agree on questions to be asked, and "clock-stop time," during which the company prepares answers to questions posed by regulators. Additionally, in case of a negative CHMP opinion, a company may request a re-examination procedure that is not subject to clock-stop time. The third factor concerns the calendar time that combines both the active and clock-stop time, and, where relevant, the re-examination time. Furthermore, the MA applicant size was determined through the employee headcount and total revenue in the year of approval using the Scrip 100 League Tables 2006–2016 (https://scrip.pharmamedtechbi.com/scrip100/home) or, alternatively, a company's annual report. Companies were considered a small or medium-sized enterprise if they employed fewer than 250 people and their total revenue did not exceed 50 million euros, in line with a recommendation by the EC,[20] or if no information could be identified. Other companies were considered "big pharma."

Data analysis

We described obligations, the number, type, and timing of changes made to them and the timing of data submission. RRs and 95% confidence intervals were calculated using the Wald method to assess the association between potential factors and change to obligations, for which we used a cutoff of ≤0.66 or ≥1.5. Because the cohort of obligations studied is not a subset but the complete population and the absolute number of obligations is small, significance testing was deemed less relevant. All calculations were performed using R version 3.4.2 and RStudio Desktop version 1.1.383.

SUPPORTING INFORMATION

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

Table S1. Characteristics of conditionally authorized medicines for which specific obligations were included.
Table S2. Description changes in specific obligations, with assessment of impact on the initially requested activities and reasons for change (n = 22).
Table S3. Drug-related, procedure-related, and obligation-related factors possibly impacting obligation changes.
Box S1. The Conditional Marketing Authorisation pathway in the EU
Data S1. Supplementary material references

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CONFLICTS OF INTEREST

All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: H.L. is past-chairman of Dutch Medicines Evaluation Board and past-member of the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). M.B. is director of the Copenhagen Centre for Regulatory Science (CORS), based at the University of Copenhagen. CORS is a cross-faculty university anchored institution involving various public (Danish Medicines Agency, Copenhagen University) and private stakeholders (Ferring

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AUTHOR CONTRIBUTIONS

L.B., A.M., H.L., M.B., O.K., and J.H. wrote the manuscript. L.B., A.M., H.L., O.K., and J.H. designed the research. L.B. and J.H. performed the research. L.B. and J.H. analyzed the data.

DISCLAIMER

The views expressed in this article are the personal views of the authors and must not be understood or quoted as being made on behalf of or reflecting the position of the Dutch Medicines Evaluation Board or the European Medicines Agency or one of its committees or working parties.

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