



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Conditional marketing authorisation

Report on ten years of experience
at the European Medicines Agency

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Abbreviations used in the report

6MWT	6 minute walking test
ASCT	Autologous stem cell transplantation
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional marketing authorisation
CNS	Central nervous system
CR	Complete response
CSR	Clinical study report
EMA	European Medicines Agency
EPAR	European public assessment report
MA	Marketing authorisation
MAH	Marketing authorisation holder
MRCC	Metastatic renal cell carcinoma
ORR	Objective response rate/ overall response rate
OS	Overall survival
PA	Protocol assistance
PEP	Primary endpoint
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PSUR	Periodic safety update report
QOL	Quality of life
SA	Scientific advice
SO	Specific obligation(s)

Executive summary

This report summarises the experience with conditional marketing authorisations since the first use of this tool in 2006 up to 30th of June 2016 (the cut-off date for this report). During this period 30 conditional marketing authorisations have been granted, of which 11 have been converted into “standard” marketing authorisations, 2 have been withdrawn for commercial reasons and the remaining 17 authorisations are still conditional. None of the marketing authorisation have been revoked or suspended. For the authorisations that are still conditional, none have been authorised for longer than five years. Although the number of authorisations granted (as well as numbers of unsuccessful CMAs) does not show a dramatic increase in numbers over the years, it seems that the interest in this authorisation route is increasing.

Just under half (14/30) of conditional MAs granted were proposed as such by the applicant in the initial submission, indicating certain reluctance on the applicants’ side. On the other hand, the higher number of CMAs actually granted indicates that the CHMP have carefully considered when this authorisation type would be appropriate.

Over the review period the number of “unsuccessful” CMAs was slightly lower (22) than of CMAs granted (30). In all cases a reason for not accepting conditional MAs when such possibility was discussed by the CHMP was consideration that the benefit–risk balance is negative, only in some cases complemented by the conclusion that other criteria¹ for granting a CMA were also not met. Interestingly, the “unsuccessful” CMAs represented a wider range of therapeutic areas, while only few therapeutic

areas (oncology, infectious diseases, neurology and ophthalmology) have been successful in applying the CMA authorisation route.

Relatively frequently the conditional authorisation type was first considered only during the assessment of the application, which was linked with longer total duration of the procedure. In this context it is advised for the MAHs to engage in early dialogue and apply a prospective planning of CMAs, which is expected to support prompt assessment of such applications, and could also facilitate prompt completion of additional studies and timely availability of comprehensive data.

As basis for granting CMAs, typically results from two main/pivotal studies of phase II or III were provided, which in most cases were open label, randomised and measured a pre-defined response rate. The concept of CMA foresees that limited data for initial authorisation is complemented by additional data generated in the imposed specific obligations, in order to bring the overall data available to a comprehensive level. Specific obligations imposed by the CHMP for CMAs almost exclusively concerned submission of results from clinical studies. Those studies in most cases were already ongoing at the time of their imposition and almost all had generation of efficacy and safety data among the objectives. On average approximately two studies were imposed, typically open label phase II, III or IV studies, either randomised or single arm, and the majority had a primary endpoint different from that used in the main/pivotal studies for the initial authorisation. These studies usually required data with longer treatment and/or follow-up duration and similar or larger sample size, as compared to previously provided main/pivotal studies. The totality of data provided for initial authorisation and imposed as specific obligations almost always included phase III (or IV) study/-ies,

1 In four cases the CHMP explicitly concluded that benefits of early access do not outweigh the risks, in 2 cases that unmet medical needs will not be fulfilled, and in one case that it is unlikely that the applicant will be able to provide comprehensive data post-authorisation

comparative data (vs. active control and/or placebo or background therapy control) and, apart from some products mainly in oncology area, blinded study data.

Most specific obligations did not have any changes to their scope and due dates. Only few had major changes to the scope (3/87) and/or extension beyond one year (11/87). Although often the changes in scope and timelines of specific obligations were related to difficulties in recruitment and study initiation or conduct, in some cases it was linked to better-than-expected outcomes (e.g. lower than expected incidence of metastases or longer overall survival). The due dates for submission of data from specific obligations were generally observed and often (20/61) data were submitted more than a month early.

Conditional marketing authorisation is seen as an important tool for fostering early access to medicines for patients, bringing forward the authorisation before comprehensive data is available, which on average took about four years. Nevertheless, further improvements in its application are still possible. In particular, early dialogue and timely preparation for conditional applications could support prompt assessment and generation of the required post-authorisation data, and further efforts could target those therapeutic areas that so far have not been successful in applying this regulatory tool.

Introduction

With adoption of Regulation (EC) No 726/2004, a new provision was introduced in Article 14(7) – a renewable marketing authorisation that is valid for one year and is subject to specific obligations. This provision was further elaborated in the Commission Regulation (EC) No 507/2006 (referred to as Commission Regulation in the text), setting the scope and criteria for granting such authorisations, as well as regulating other aspects of this authorisation type. In accordance with Article 11 of Commission Regulation, the EMA had to develop guidelines concerning the scientific application and the practical arrangements necessary to implement this authorisation type – these were developed by the CHMP and the latest version has been adopted by the CHMP on 25 February 2016 (referred to as CHMP Guideline in the text).

The following categories of products fall within the scope of Commission Regulation according to the provisions of Article 2, and could be potentially be eligible for a conditional marketing authorisation:

1. medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;
2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC;
3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.

For a product to be granted a conditional marketing authorisation it must fulfil all of the criteria set out in Article 4(1) of the same Regulation:

- (a) the risk–benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;
- (b) it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- (c) unmet medical needs² will be fulfilled;
- (d) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Further information and guidance on the requirements for granting, renewal and other aspects of conditional marketing authorisations can be found in the respective CHMP Guideline³ and the procedural and regulatory advice on the EMA website. Article 14(7) of Regulation (EC) No 726/2004 came into force in November 2005, and the Commission Regulation – in April 2006. The first conditional marketing authorisation (Sutent) was recommended by the CHMP on 27 April 2006 and the authorisation was granted by the European Commission on 19 July 2006.

The aim of this report is to provide detailed information on the experience accumulated with conditional marketing authorisations over the first 10 years. It comprises of summary of various aspects of this experience in the body of the report, and more detailed information at product level in Annexes to this report.

² Article 4(2) of the Commission Regulation defines 'unmet medical needs' as a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected

³ Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 (EMA/CHMP/509951/2006, Rev.1), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/03/WC500202774.pdf

Methods

Since the number of products included in the analysis is limited, this report contains only descriptive summaries of experience and no analysis of statistical significance of the findings has been performed. More detailed information on the products included in this analysis (including elements used in summary statistics presented in this report) can be found in Annexes to this report, as well as in the European Public Assessment Reports published on the EMA website.

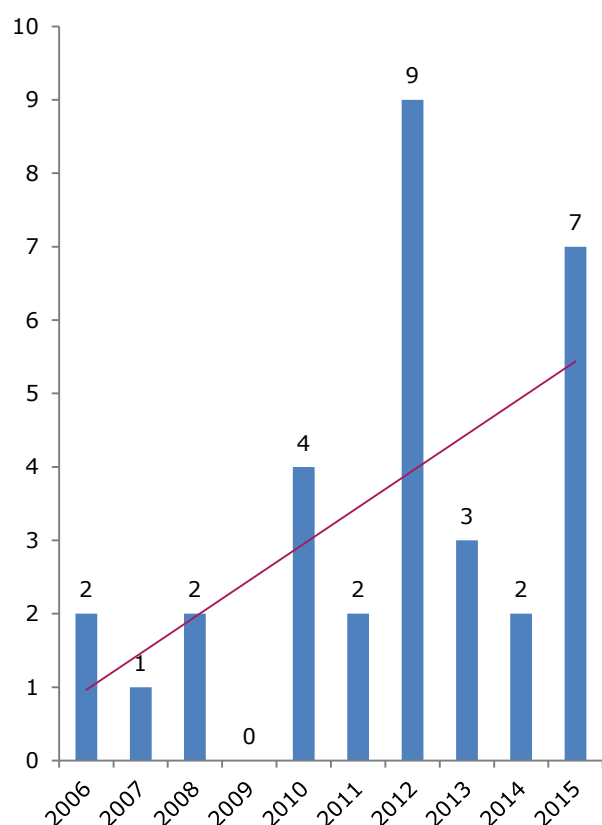
The data used in this report is mainly based on the information published in the European Public assessment reports (EPAR), but is also complemented with further information included in other assessment reports (not published as part of the EPAR) and some details in the applications submitted by the applicants (mainly clinical study reports, risk management plans and justification for requesting conditional marketing authorisation).

All data presented in this report refers to the time period from 01 July 2006 till 30 June 2016, unless stated otherwise.

Interest in conditional marketing authorisation

The numbers of marketing authorisation applications requesting conditional approval at the stage of initial submission is presented in the Figure below. On average the numbers have been increasing; however, this trend is somewhat unstable with years of considerably more requests (e.g. 2012) followed by years when the number of requests is much lower (e.g. 2013 and 2014).

Figure 1. Number of applications requesting conditional marketing authorisation at submission, by year of submission

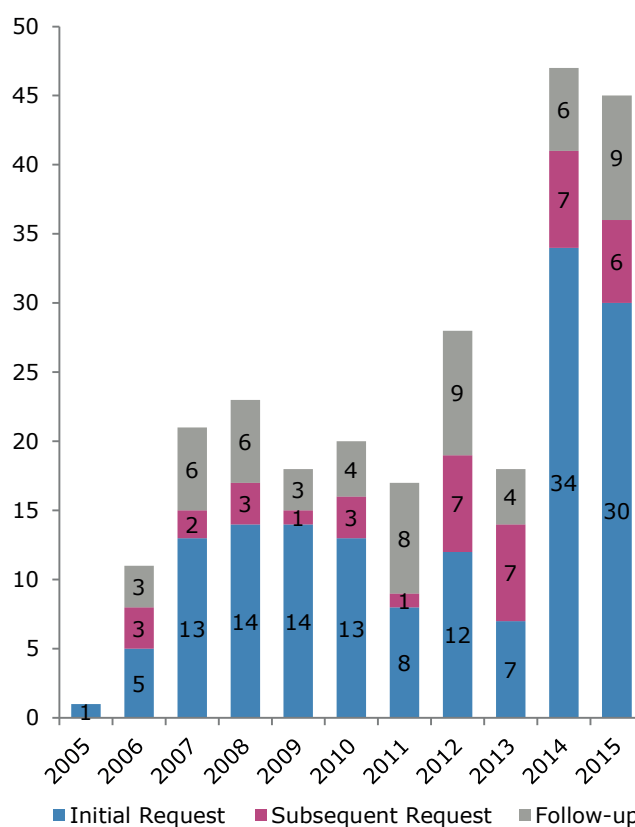


Note: Includes only applications for CMA submitted till 2015 and resulting before end of 2016 in a positive or negative opinion, or a withdrawal of the application after adoption of the list of questions by the CHMP

In addition to marketing authorisation applications made specifically for conditional approval, the interest in this authorisation route

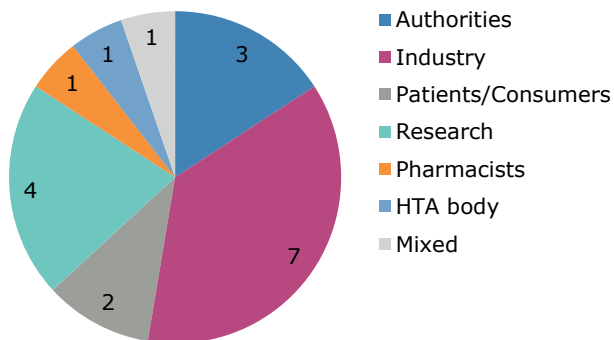
is demonstrated also by scientific advice and protocol assistance requests, where the scope of the advice concerns potential conditional marketing authorisation. The figure below shows the number of such advice procedures per year up until December 2015. Overall, the number of advice procedures is considerably higher than the number of marketing authorisation applications received. In addition, a marked increase in number of requests has been observed recently, in 2014 and 2015.

Figure 2. Number of scientific advice or protocol assistance requests, where the scope of advice has been identified as concerning conditional marketing authorisation, by year of procedure start



Initial request – first request on a particular product, subsequent request – repeated request for a product, but with a different scope, follow-up – follow-up request on the same product and similar scope of question(s) as previously

Figure 3. Affiliation of sources of sets of comments received during public consultation in 2015 on CHMP Guideline concerning conditional marketing authorisation (N=19)



A public consultation was conducted in 2015 on the revised CHMP Guideline concerning conditional marketing authorisation. It attracted a considerable interest and EMA received 19 sets of comments from various stakeholders, including a total of 53 general comments and 121 specific comments on the text of the draft Guideline. Of the specific comments on the text more than a half (64) concerned Guideline section 4.1.2 addressing the requirements that have to be met for granting a CMA. Other topics popular in comments include the extent of use of conditional MA route, a conditional authorisation of new indications, early dialogue, transparency, and compliance with obligations. An overview of the comments has been published on the EMA website⁴.

High interest in the conditional marketing authorisations and its relevance in the context of timely access to medicines have also led to it being discussed in various fora, including the European Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP"), and being referred to in conclusions of the Council of the European Union on strengthening the balance in the pharmaceutical systems in the EU and its Member States⁵.

4 Overview of comments received on 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004, EMA/647097/2015, http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2016/03/WC500202628.pdf

5 <http://www.consilium.europa.eu/en/press/press-releases/2016/06/17-epsco-conclusions-balance-pharmaceutical-system/>

Conditional marketing authorisations granted

General characteristics

Since 2006, a total of 30 conditional marketing authorisations have been granted. Of these, two have been subsequently withdrawn (both withdrawals concerned pandemic influenza vaccines and both withdrawals were made for commercial reasons), eleven have been converted into marketing authorisations not subject to specific obligations ("standard"/"full" authorisations) and the remaining are still conditional marketing authorisations.

have not been active or successful in using the conditional authorisation route. These areas include, for example, cardiovascular diseases, endocrinology, respiratory medicine and rheumatology.

Just over a half of conditional authorisations were in oncology area, followed by almost a third for infectious diseases, the remaining products being for neurology or ophthalmology indications. It is evident that certain therapeutic areas, although being represented in the overall portfolio of centrally authorised products,

Figure 4. An overview of conditional marketing authorisations granted by the year of authorisation and current status

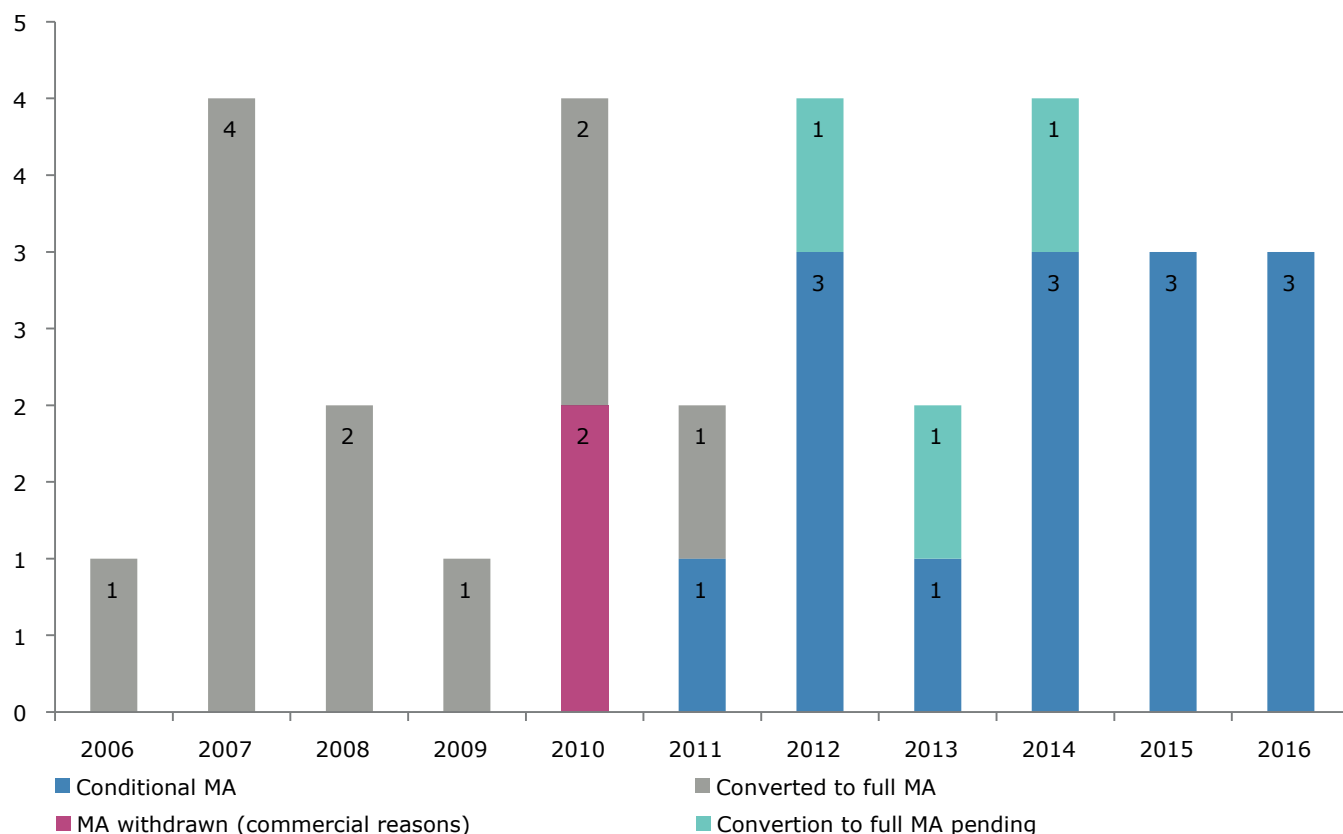
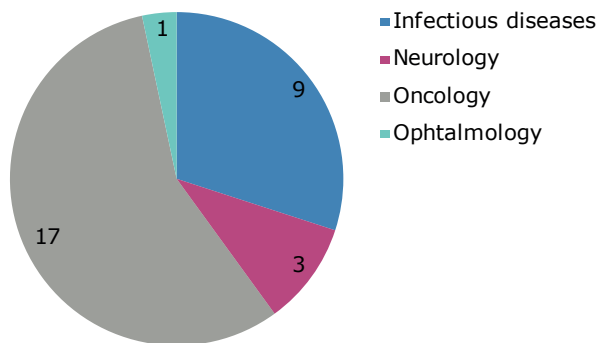
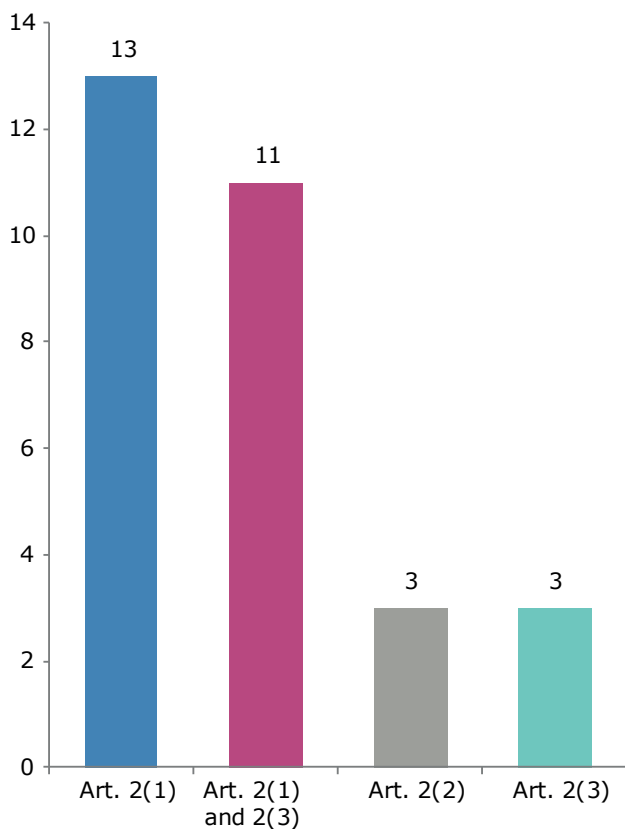


Figure 5. Conditional marketing authorisations by the therapeutic area (N=30)



Regarding the scope of products for which a conditional marketing authorisation is possible (as defined in Article 2 of Commission Regulation), almost half of the products were orphan (14/30, Art. 2(3)) at the stage of initial assessment, while large majority (24/30) were for seriously debilitating or life-threatening conditions (Art. 2(1)). Only three products fell into scope as products for use in emergency situations (Art. 2(2), all influenza pandemic vaccines).

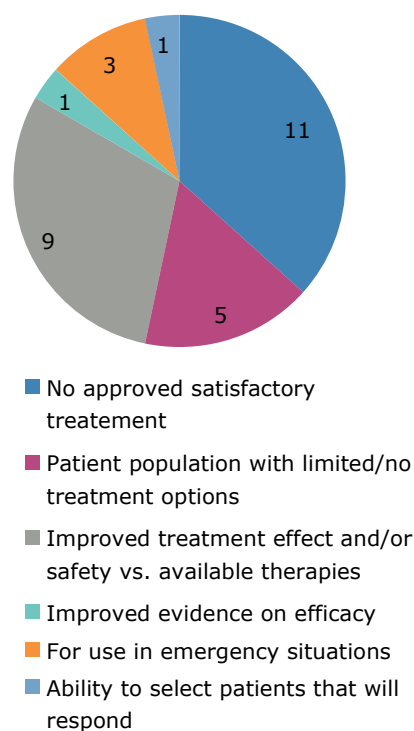
Figure 6. Categories of scope for conditional marketing authorisations (N=30)



One of the requirements for granting a conditional marketing authorisation is that

an unmet medical need⁶ is to be fulfilled by the product concerned. The reasons for this of course differ in each individual case, but the main categories of how unmet medical needs have been expressed when justifying this requirement are summarised in the figure below. In just over a half of the cases (16/30) justification as primary reason quoted limitations of available treatment (no (satisfactory) treatments), while in almost one third of cases – the added value of the product versus available therapies.

Figure 7. Categories of medical need(s) addressed by the CMA products (N=30)

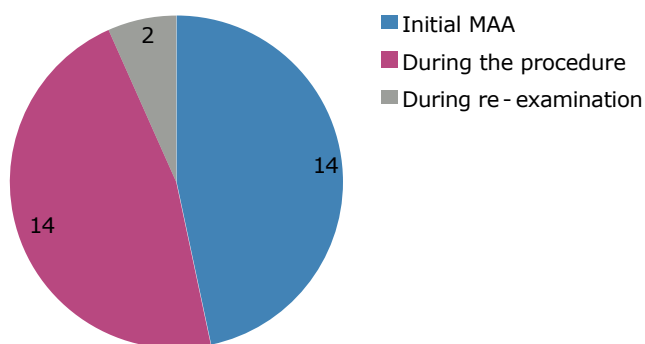


⁶ Article 4(2) of Commission Regulation defines unmet medical needs as a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected. Scientific elements of assessment of this criterion are further elaborated in the CHMP Guideline.

Authorisation process

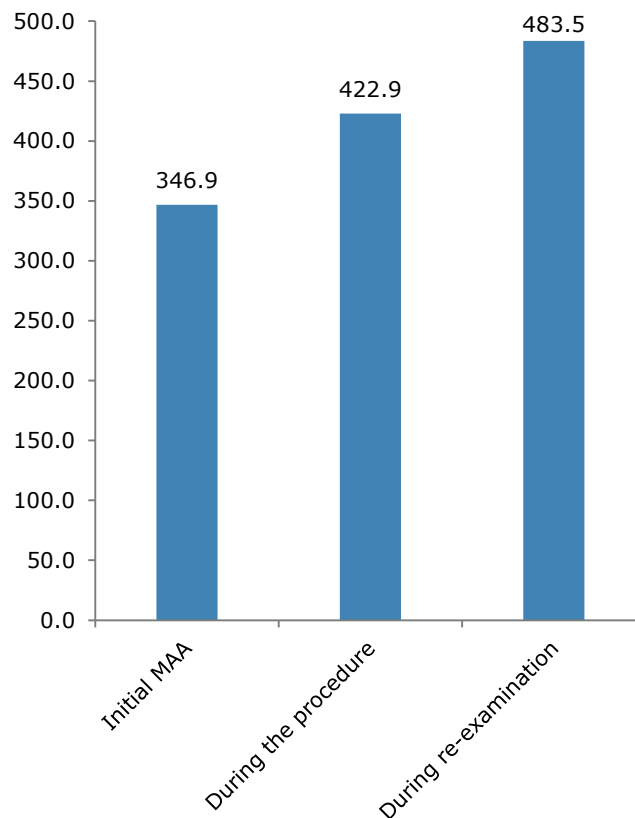
Just under half (14/30) of applications that eventually resulted in granting of a conditional marketing authorisation contained a proposal for this authorisation type in the initial submission from the applicant. In other cases the proposal for a conditional authorisation was made either during the initial assessment (14/30) or at the re-examination stage (2/30). This likely indicates a certain reluctance of applicants to proactively propose a conditional authorisation type already in the initial application.

Figure 8. Stage of assessment procedure, when conditional marketing authorisation was first considered, all conditional marketing authorisations granted (N=30)



Unsurprisingly, later consideration of conditional marketing authorisation was linked with longer total duration of the assessment procedure (including clock-stops). Average (mean) combined duration of assessment and clock-stops is presented in the figure below, while median duration showed similar differences (323, 407 and 483.5 days for initial application, assessment procedure and re-examination, respectively). The average assessment and clock-stop duration for all positive opinions in centralised procedure in 2015 was 202 and 131 days, respectively⁷. It has to be noted that only three conditional marketing authorisations were granted following accelerated assessment (Darzalex, Isentress, Tagrisso), and the combination of these two early access tools has been now encouraged in a revised CHMP guideline.

Figure 9. Average duration of assessment procedure (days from procedure start to CHMP Opinion, including clock-stop) by stage of procedure when conditional MA first considered (N=30)



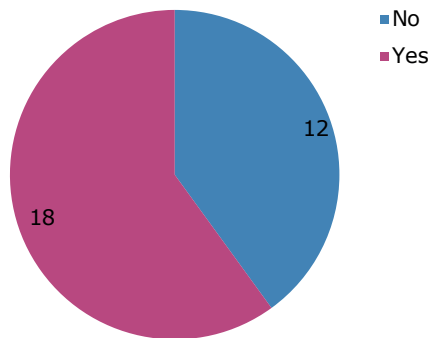
Duration of procedure – time from start date of assessment till adoption of final CHMP opinion (without exclusion of time allowed for preparation of responses or oral explanation)

⁷ Please see EMA Annual Report 2015 (http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2016/05/WC500206482.pdf)

Previous scientific advice or protocol assistance

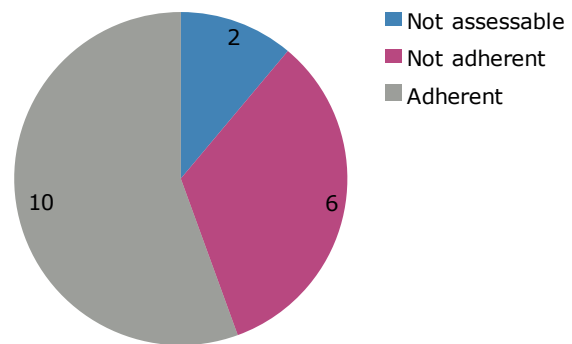
The majority (18/30) of the products eventually granted conditional marketing authorisation received a CHMP scientific advice or protocol assistance prior to submission of the initial application.

Figure 10. Scientific advice or protocol assistance prior the MAA submission (N=30)



An analysis of adherence to scientific advice/protocol assistance has been conducted in respect to the choice of primary study endpoint(s), comparator(s) in the study and the statistical methods. Of the 18 products with previous SA/PA, two had not discussed these aspects, but of the remaining products the majority (10/16) were adherent to the SA/PA in respect to the above mentioned aspects. Six products did not to some extent follow the previously obtained SA/PA, but still eventually obtained the authorisation – the differences are summarised in the table further below.

Figure 11. Adherence to SA/PA in the MAA submission, all CMAs with SA/PA (N=18)



Not assessable = SA/PA did not concern aspects of development used for estimation of adherence (endpoint, comparator, statistical methods)

Table 1. Non adherence to previous scientific advice/ protocol assistance

Product name	Primary endpoint	Comparator	Statistical methods
Prezista	Proposed primary efficacy endpoint "time to virological failure" accepted at SA, although considered a deviation from clinical practice in the heavily pretreated patient population. Applicant changed endpoint to virologic response.	Adherence	N/A
Tyverb	Adherence	N/A	Company proposed an interim analysis. CHMP agreed, however not with regards to TTO effect size which would be too premature. No change made by the company
Cayston	Company proposed to use FEV1 as PEP. CHMP agreed with FEV1 evaluation at week 4, 12 or 24. Company, however, amended the protocol and included the QOL cystic fibrosis questionnaire as PEP.	Adherence	N/A
Caprelsa	Adherence	Company proposes placebo control. CHMP advised for best standard of care or best investigators option (chemotherapy) superiority, or superiority with BIO as background therapy add on. Company did not amend the study accordingly.	N/A

Product name	Primary endpoint	Comparator	Statistical methods
Pixuvri	Company proposed ORR (objective response rate), an objective CR plus PR. CHMP did not regard ORR suitable for a new chemical entity and for use in combination therapy and therefore proposed time to progression as (co-) primary endpoint. CR is part of ORR and does not allow an evaluation of time related parameters reflecting the clinical course. Company performed single pivotal study with CR and CRu as single PEP.	Adherence	Adherence
Translarna	SA: clinically meaningful effect should be demonstrated in two domains – disability and muscle strength. The Applicant uses single endpoint (6MWT 10% improvement) in pivotal study.	Adherence	SA: preference is given to the parametric approach with ANCOVA; advised that the two most important prognostic variables are selected to avoid over-stratification. Non adherence.

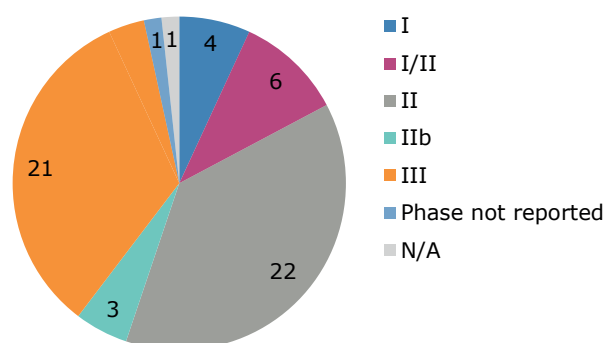
Data provided at the time of authorisation

This part of the analysis is based on studies that were identified as main/pivotal in the CHMP assessment for products authorised as CMA. Studies were identified as main/pivotal if they were labelled so explicitly in the CHMP AR, or if main results from the study were quoted in the benefit-risk discussion in the CHMP AR. On average 1.87 (median 2, range 1–5) such clinical studies were included per application. By therapeutic areas the average number of main/pivotal studies was 2.55, 1.67, 1.71 and 1 for infectious diseases, neurology, oncology and ophthalmology, respectively.

The studies were mostly phase II or phase III, just over half of them (30/58) being phase II (including phase I/II and or IIb). In largest therapeutic areas (oncology and infectious diseases) between 30 – 40% of studies were phase III (in other two areas the sample size was limited). There were relatively more phase

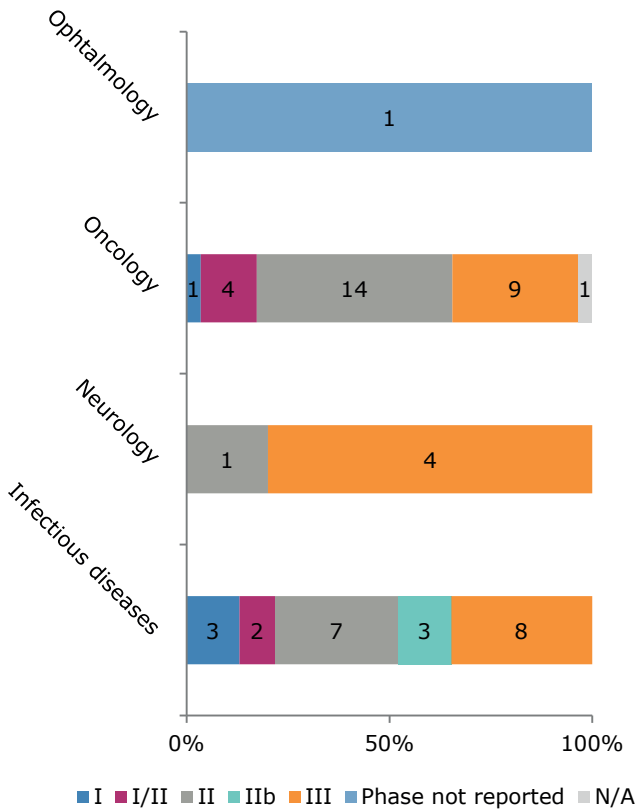
I studies in the infectious diseases area, but that was driven by data provided on one of the pandemic influenza vaccines.

Figure 12. Studies identified as main/pivotal in assessment of the applications, by phase (N=58)



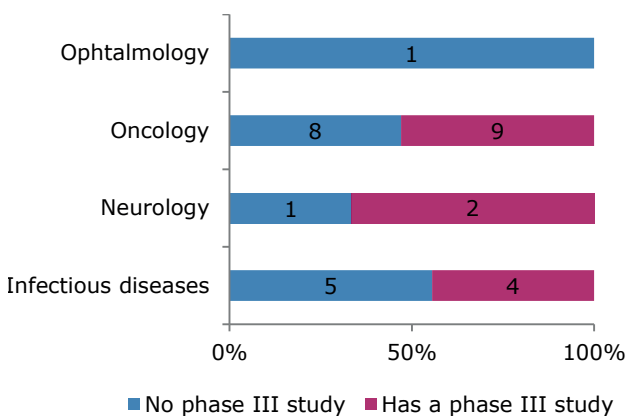
N/A – pooled data from several studies and named patient early access programmes identified as pivotal in one case

Figure 13. Relative distribution of main/pivotal studies by phase, per therapeutic area (N=58)



On the product level, half (15/30) of products had provided results from at least one phase III study (even if interim results). This proportion was similar across therapeutic areas, apart from ophthalmology (with a single product).

Figure 14. Relative proportion of product with at least one phase III main/pivotal study vs. other products (N=30)



All but one (retrospective study for Holoclar, ophthalmology area) main/pivotal studies were prospective interventional studies.

Most studies (34/58) were randomised multiple arm studies, but just over a third of studies consisted of a single arm. There were relatively more single arm studies in the oncology area (15/29) and relatively more randomised multiple arm studies in infectious diseases area (18/23).

Figure 15. Design of main/pivotal studies (N=58)

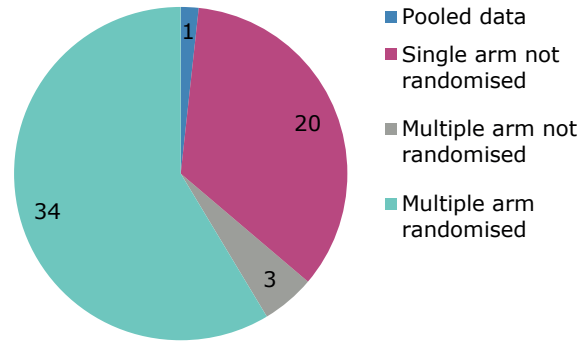
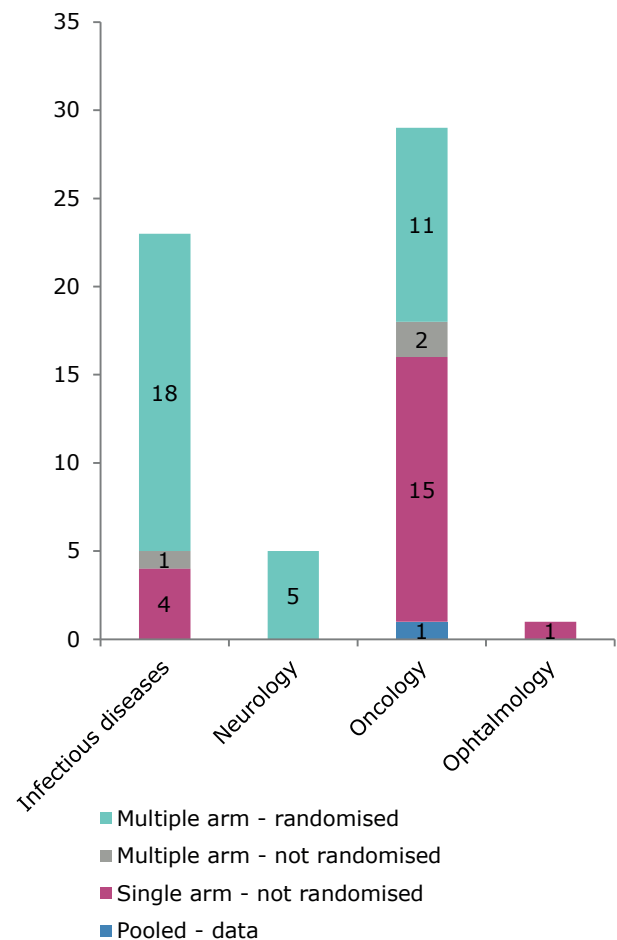


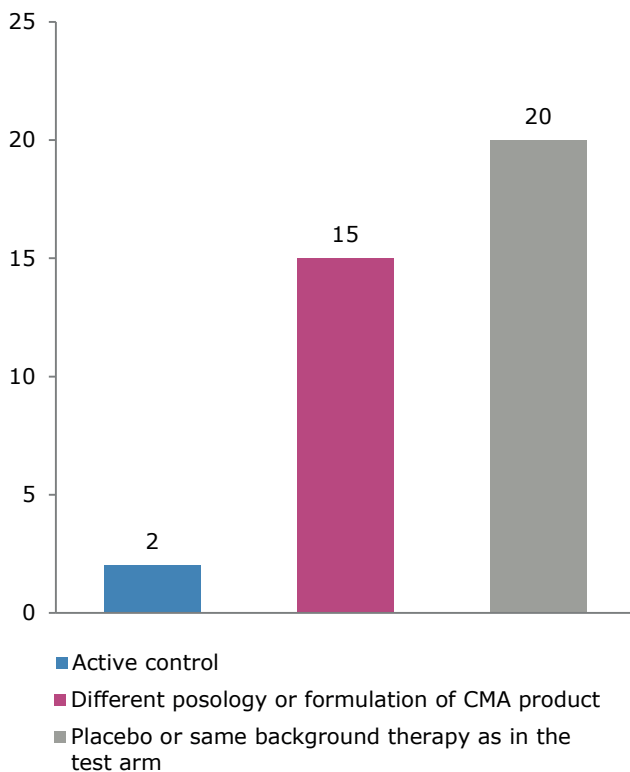
Figure 16. Study designs per therapeutic area (N=58)



Although multiple arm studies made up a relative large part of the total, these studies rarely included active control (2/37), in most

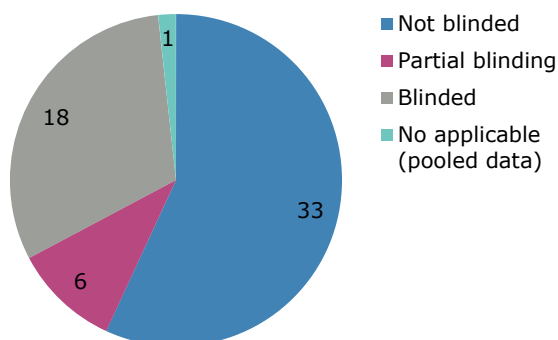
studies (20/37) the control being either the placebo or the same background therapy as in the test arm.

Figure 17. Type of control arm in multiple arm main/pivotal studies (N=37)



Slightly more than half of main/pivotal studies (33/58) were not blinded, the ratio reaching more than three quarters (22/29) in the oncology area, while in neurology all studies (5/5) were blinded.

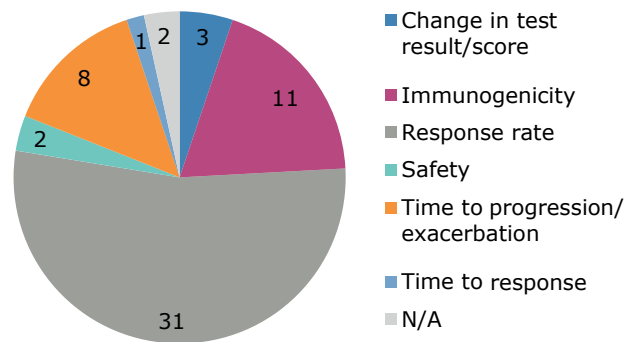
Figure 18. Blinding in main/pivotal studies (N=58)



In most cases (31/58) the primary endpoint of the study was percentage of subjects reaching certain criteria for response, as defined in the protocol (e.g. virological response).

For pandemic influenza vaccines immunology endpoints were used as main in all main/pivotal studies (11), while endpoints driven by time to disease progression (e.g. progression free survival, time to progression) were almost exclusively (7/8) applied in oncology area.

Figure 19. Types of primary endpoints in main/pivotal studies (N=58)



N/A – not applicable for the pooled analysis (1) and not applicable for a particular analysis set regarded as main/pivotal data

In almost all cases the population included in main/pivotal study/-ies was identical, very similar or slightly narrower/wider than the target population defined in the final SmPC at the time of authorisation. Only in one case a clearly different population was included in the study, which was still considered pivotal for the application. Zykadia study A2203 included cizotinib naïve adult patients with ALK-activated NSCLC, while the indication was granted for treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib. This, however, was just one of three studies that were identified as main/pivotal for this application.

The treatments co-administered with the investigational product in studies were in line with the eventual recommendations in the indication in SmPC section 4.1, with the exception of product Intelence, where main studies investigated combination therapy with darunavir, while combinations with other protease inhibitors (included in the initial indication) were investigated through specific obligations post-authorisation.

In most cases the main/pivotal studies investigated (at least one) posology eventually recommended in the SmPC. Only in 4 cases the posology investigated in a main/pivotal study differed from eventually recommended posology, of which three were studies for pandemic influenza vaccines and one study for the product Arzerra. In all these cases the posology recommended in the SmPC was investigated in other main/pivotal study(-ies) for the respective product.

Imposed specific obligations

For the purpose of this analysis specific obligations, when applicable, were split into separate activities. These in most cases corresponded to a separate entry in the list of imposed specific obligations in Annex II to the marketing authorisation, but sometimes were divided up in separate activities, if there was a clear distinction. Submission of regular updates (e.g. in PSURs) and repetitive submission of interim results, unlike one-off submission of interim results by certain concrete date, was not regarded as a separate activity for the purpose of this exercise.

The number of measures that have been imposed as specific obligations had varied, ranging from one to 16 (Vectibix) activities. In particular, the number has shown a tendency to stabilise – the average number of activities imposed has decreased, and during last three years conditionally authorised products have each had only one to four activities imposed as specific obligations.

Most of specific obligations imposed (at the time of MA or later, total N=107) pertained to submission of final results from clinical studies (77/107). Numbers of other types of activities were limited – of these mostly interim results and certain additional analyses were occasionally explicitly requested in addition to the study reports. Quality related measures were just few and reserved to products to be used in emergency situations (all influenza pandemic vaccines). Other measures included, e.g. ensuring availability of a test necessary for correct use of product, development of an additional statistical analysis plan for certain

studies or implementation of certain activities to ensure close monitoring of any development of resistance to the treatment.

Figure 20. Number of specific obligations imposed per CMA, arranged by authorisation date of the product (N=30)

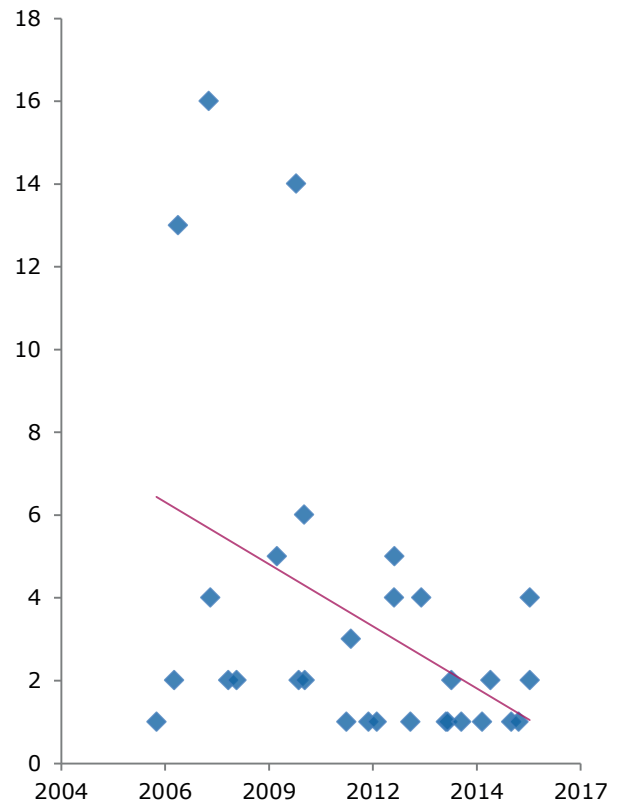
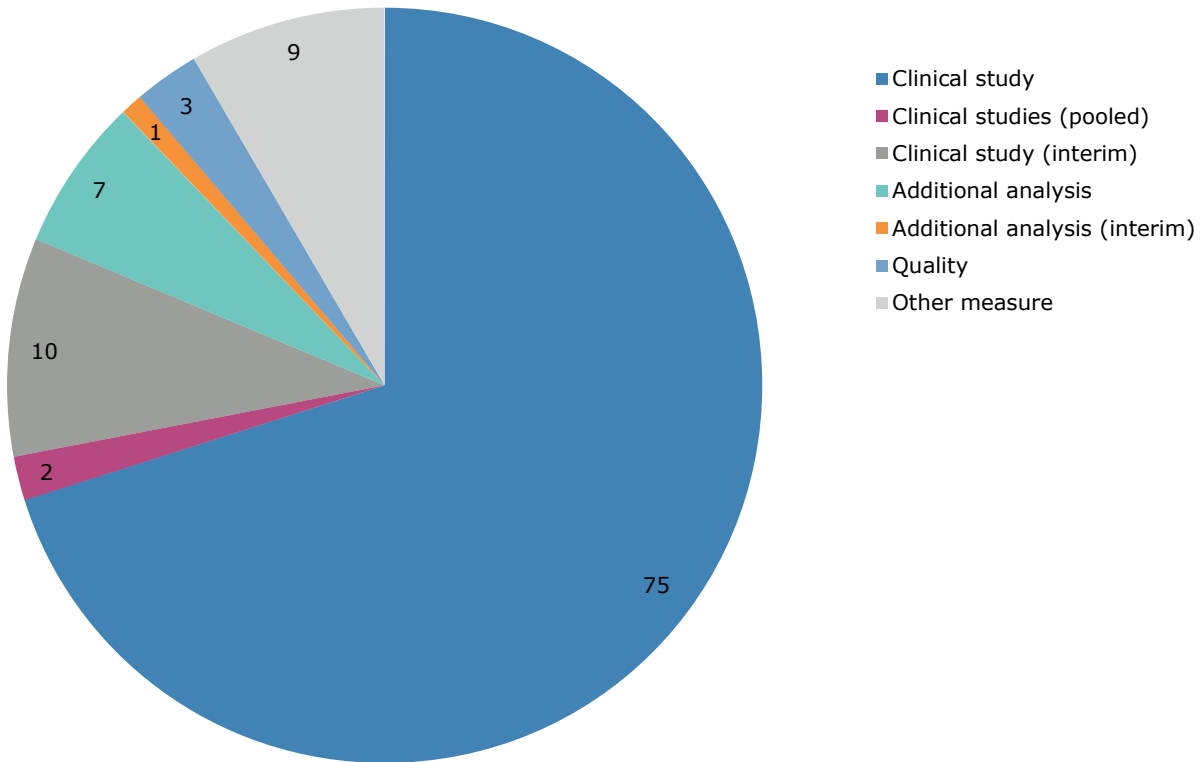


Figure 21. Categories of specific obligation, all obligations imposed (N=107)

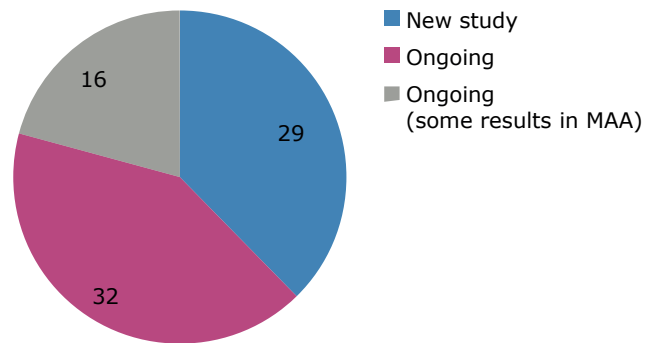


More recently imposed specific obligations tend to focus on submission of final results from clinical studies; while earlier it was more common to request in addition interim results, additional analyses and other types of activities. For example, of the 20 specific obligations imposed for new CMAs in last three years (from July 2013 till June 2016), there was only one additional analysis, one interim results and one quality related activity (all others pertained to submission of final clinical study results).

Since most of the specific obligations were related to submission of final clinical study reports and these also contributed most to generation of comprehensive data post-authorisation, further analysis focuses on submission of final (or latest requested) results from clinical studies (or a pool of studies).

At the time of imposition the majority (48/77) of studies were already ongoing, and early results from these studies were often submitted in the initial authorisation procedure. In one fifth of cases (16/77) early results from the study imposed as specific obligation served as main/pivotal data of the original authorisation.

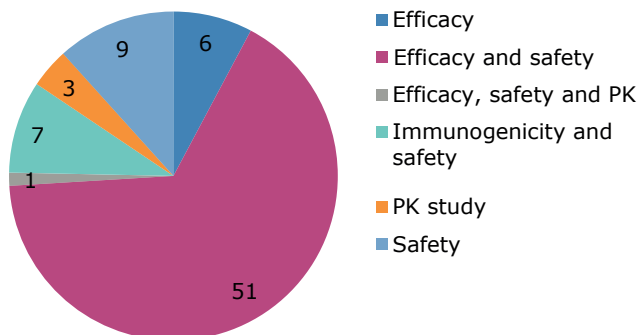
Figure 22. Status of the imposed studies at the time of CHMP opinion (N=77)



Some results in MAA – interim results included in the application as main/pivotal studies

In roughly two thirds of cases the imposed studies had main objectives to provide further data on safety and efficacy (51/77), while some others were specifically targeting efficacy (6/77) or safety (9/77).

Figure 23. Objectives of the studies imposed as SOs (N=77)



Unsurprisingly, on average studies of more 'mature' phases were imposed as specific obligations, when compared to main/pivotal studies available at the time of authorisation. Nevertheless, a third of studies imposed (25/77) were earlier than phase III. This proportion was roughly similar in two larger therapeutic areas (31% and 35% for infectious diseases and oncology, respectively).

Figure 24. Clinical studies imposed as specific obligations, by study phase (N=77)

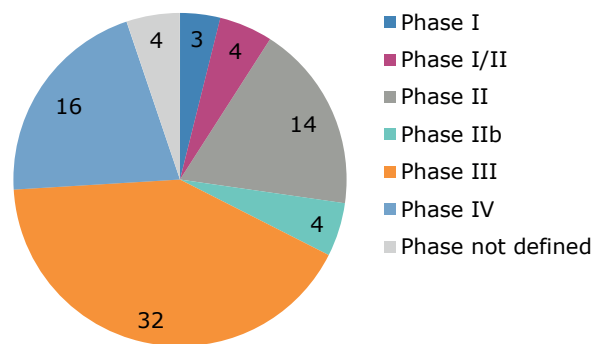
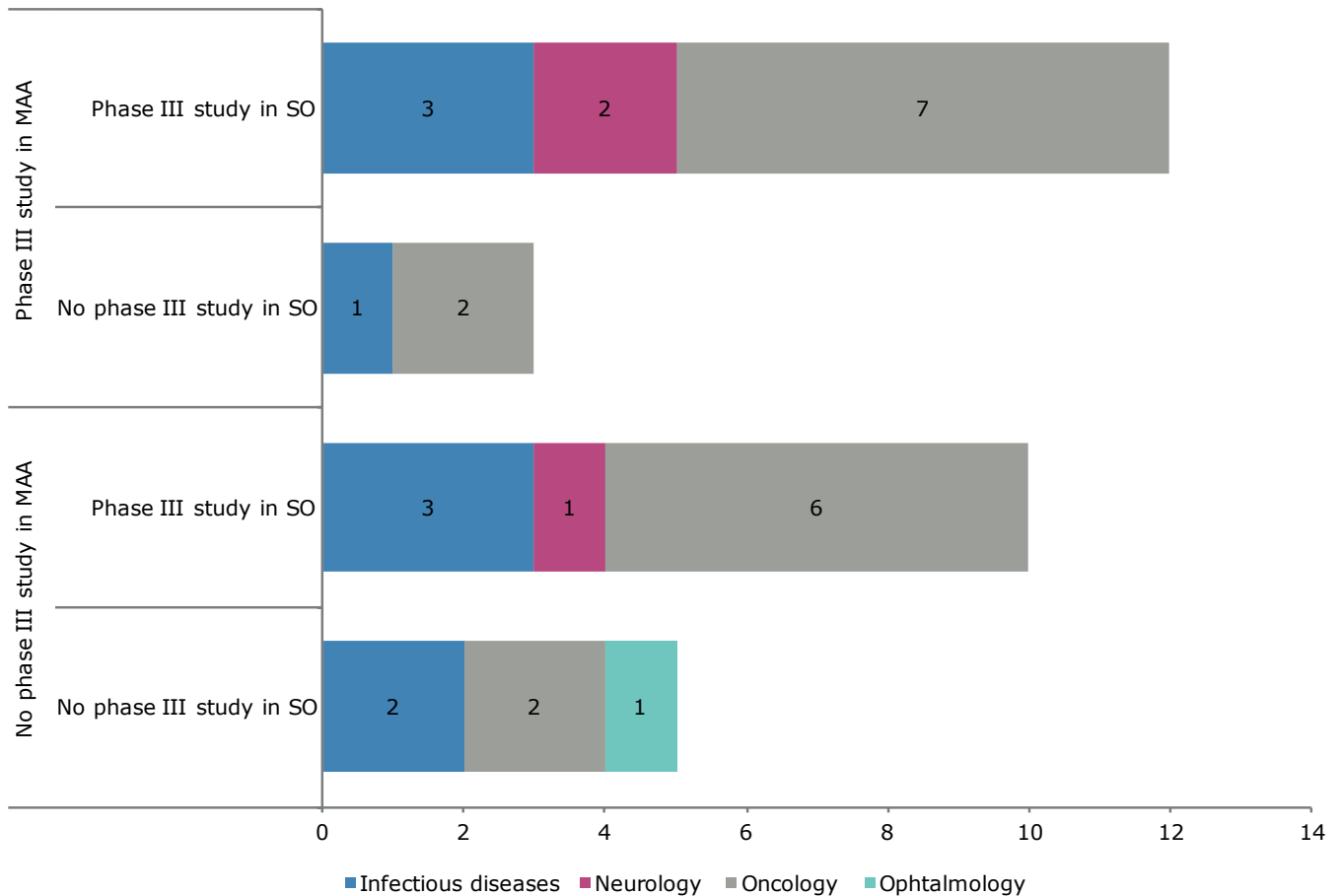


Figure 25. Imposition of phase III studies as specific obligations, by therapeutic area and presence of data from phase III study as basis for initial authorisation (N=30)



Almost all (25/30) products had results from at least one phase III study either provided at the stage of authorisation, or imposed as specific obligation. Three other products had at least one phase IV study imposed as a specific obligation and of remaining products Holoclar did not have the phase of imposed study specified (it was a “multinational, multicentre, prospective, open-label, uncontrolled interventional study”) and Erivedge had a phase II study imposed as specific obligation (albeit much larger than the initially submitted study, 800 vs. 104 patients).

Over a third of studies imposed were single arm (28/77). The proportion of single arm studies was slightly higher in the oncology area (17/37).

Although some of the imposed studies were single arm, most products had at least one multiple arm study with active control, placebo control or background therapy in the control group, provided either in the initial application, or imposed as specific obligation. No such

study was provided or requested only in some cases with no approved satisfactory treatment (n=4) and for one product for use in emergency situations.

Figure 26. Study designs of imposed studies (N=77)

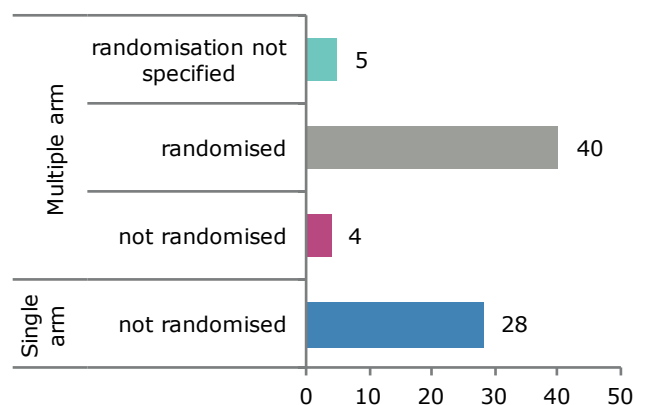
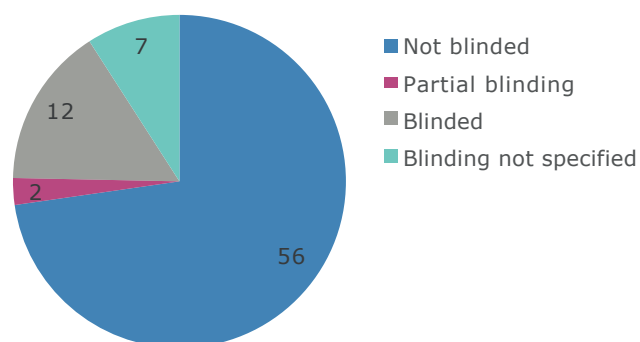


Table 2. Products with at least one study with active or placebo/background therapy control arms, studies submitted in MAA and studies imposed as SOs, arranged by category of unmet medical need(s). Products shown in bold contain such study/-ies (also) as part of main evidence for initial MA.

Category of unmet needs	At least one study with control arm(s)	No study with control arm(s)
Ability to select patients that will respond	Vectibix	
For use in emergency situations	Arepanrix Humenza	Pandemic influenza vaccine H5N1 MedImmune
Improved evidence on efficacy	Xalkori	
Improved treatment effect and/or safety vs. available therapies	Blincyto Cayston Cometriq Darzalex Diacomit Sutent Tagrisso Tyverb Votrient	
No approved satisfactory treatment	Arzerra Caprelsa Fampyra Pixuvri Translarna Votubia Zykadia	Adcetris Bosulif Erivedge Holoclar
Patient population with limited/no treatment options	Deltyba Intelence Isentress Prezista Sirturo	

Figure 27. Blinding in the imposed clinical studies (N=77)



More than two thirds of studies were open label (56/77) and this proportion was slightly higher in oncology area (31/37), but much lower in neurology (1/4).

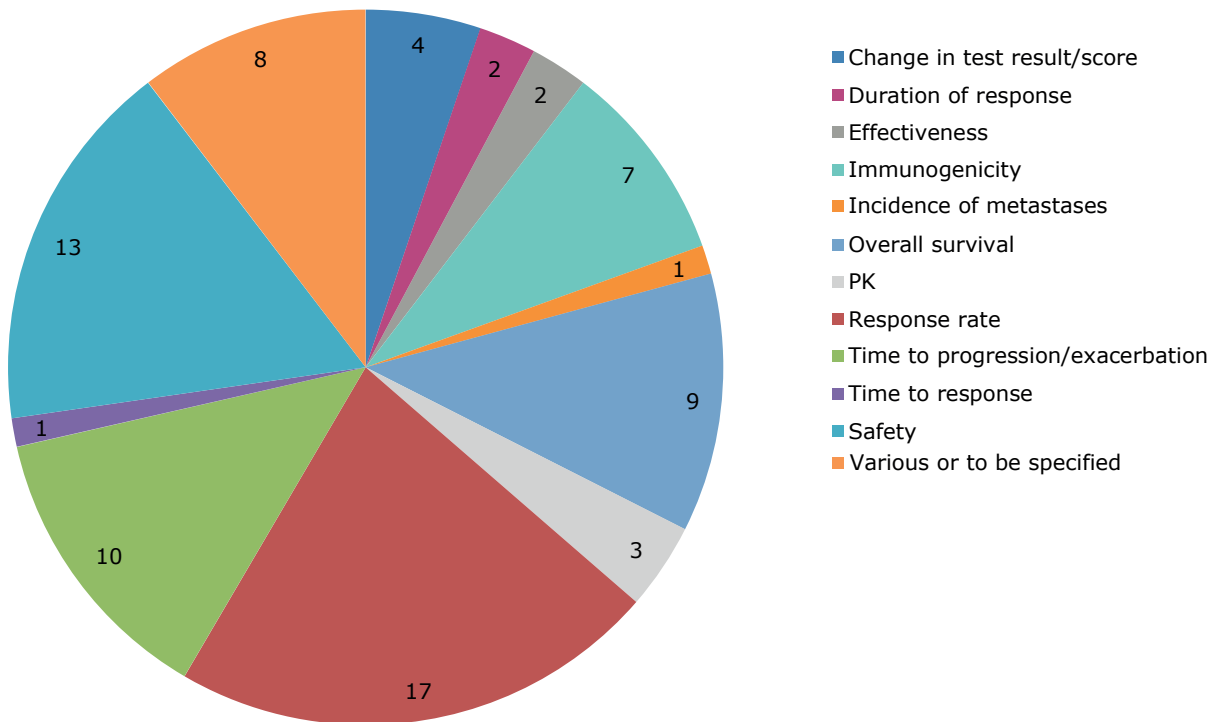
Although majority of imposed studies were not blinded, most (16/30) products had at least one blinded or partially blinded study provided in MAA submission and/or imposed as a specific obligation. Apart from two pandemic influenza vaccines and an ATMP product, all other products without a blinded or partly blinded main study or SO study were in oncology area.

Table 3. Products with at least one blinded or partially blinded study submitted in MAA and/or imposed as SOs, arranged by therapeutic area

Therapeutic area	At least one blinded or partially blinded study	No blinded or partially blinded study
Infectious diseases	Arepanrix Cayston Delyba Intelence Isentress Prezista Sirturo	Humenza Pandemic influenza vaccine H5N1 MedImmune
Neurology	Diacomit Fampyra Translarna	
Oncology	Caprelsa Cometriq Pixuvri Sutent Votrient Votubia	Adcetris Arzerra Blinicyto Bosulif Darzalex Erivedge Tagrisso Tyverb Vectibix Xalkori Zykadia
Ophthalmology		Holoclax

In the studies imposed as specific obligations in most cases the population to be included was the same or quite similar to the target population defined in the indication of the product (or a subset of that population). Only in 3 (2 for Vectibix and 1 for Sutent) of the 77 studies the population to be included was different from the target populations of the indication (though remained within the same condition) – all three were studies already ongoing at the time of granting MA and included treatment naïve patients (while the indications granted were for later lines of treatment).

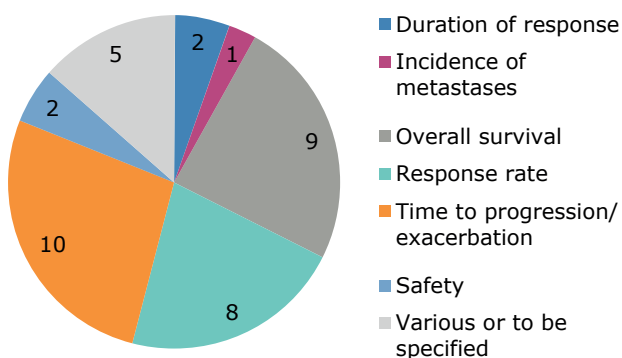
Figure 28. Categories of primary endpoints, all studies imposed as specific obligations (N=77)



An analysis has been conducted on the “primary endpoints” of imposed studies – for the purpose of this exercise defined as either the endpoint specified in the specific obligation, or, if not specified, the primary endpoint defined in the study protocol. A sixth (13/77) of imposed studies had a safety focused primary endpoint. Overall, the types of study endpoints were more variable than in the main/pivotal studies provided for initial authorisation.

in oncology a quarter (9/37) of studies were focused on overall survival, on which no product had mature data at the time of initial authorisation). At the same time in other cases the endpoint of imposed studies was identical or similar to endpoint for the data at MA stage (e.g. progressions free survival for certain products in oncology area, or immunogenicity data for vaccines).

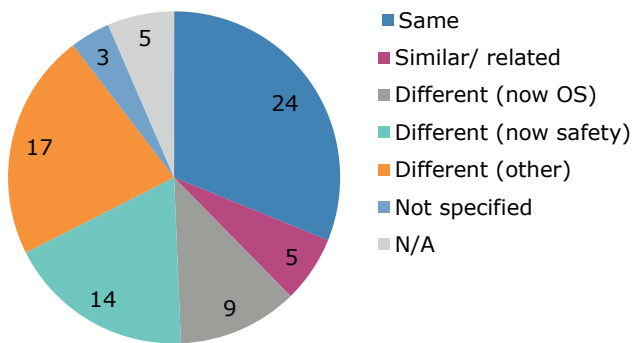
Figure 29. Categories of primary endpoints, all studies imposed as specific obligations in oncology area (N=37)



Overall, when comparing the main endpoints of imposed clinical studies with the main endpoints of the pivotal evidence at the time of authorisation, for more than one third (29/77) of studies the endpoint was the same or related (i.e. measuring the same type of effect, e.g. proportion of subjects with confirmed culture conversion instead of previous time to culture conversion). Approximately half of the studies (40/77) had a different endpoint, of which most often the difference was driven by the new endpoint being related to safety (14/40) or overall survival (9/41, of oncology studies with different endpoint 9/24).

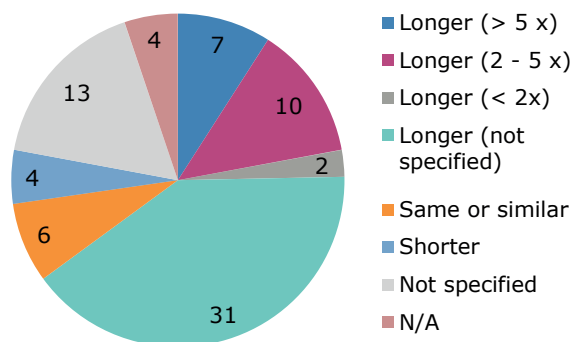
Is some cases the endpoints were focused on outcomes, that were longer-term (e.g.

Figure 30. Comparison of primary endpoint in studies imposed as specific obligations vs. primary endpoint used in main/pivotal studies at the time of authorisation (N=77)



The duration of treatment and follow-up in studies imposed as specific obligations (based on wording of the SO and information available at the time of imposition) in majority of cases (50/77) was clearly longer than treatment and follow-up duration used for primary analysis in main/pivotal studies at the time of MA. Only in very few cases the requested study was clearly of shorter duration (4/77) or the same or similar duration (6/77). In the remaining cases the duration based on scope of SO and information available at the time of MA could not be classified into either "longer" or "shorter" categories (13/78), or the comparison was not appropriate (4/78 – PK studies in healthy volunteers and a non-interventional case control study).

Figure 31. Duration of follow-up for main analysis in imposed studies vs. main/pivotal studies provided for MA (N=77)



Amendments to the specific obligations

The majority of specific obligations (69/83 of all (completed or currently pending) obligations, 47/57 of completed obligations) did not require any changes to their scope (description of the content of the specific obligations in Annex II to the marketing authorisation, excluding changes in due dates only). In some cases minor changes were introduced (e.g. inclusion of an explicit requirement that the study should be non-interventional or that the protocol should be agreed by the CHMP, or change in the time-point for primary analysis).

Only 3 specific obligations had major changes to the scope – the details are presented in the table further below, together with two specific obligations that were imposed post-authorisation and four other obligations which post-authorisation were re-classified as no longer required for the data to be considered comprehensive (re-classified to other types of post-authorisation measures).

Figure 32. Changes to scope of specific obligations, all SOs (completed or pending) (N=84)

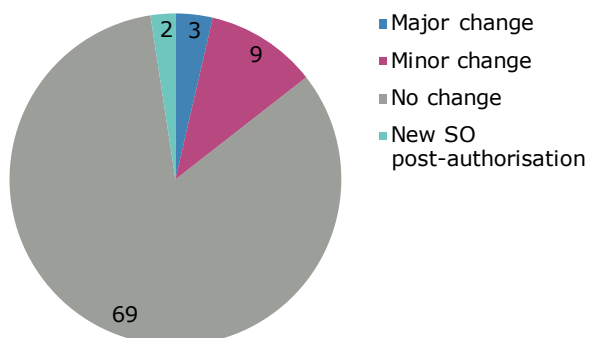


Figure 33. Changes to scope of specific obligations, SOs completed by cut-off date (N=57)

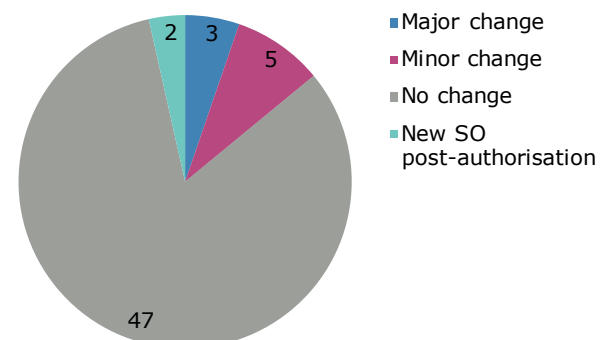


Table 4. Description of major changes, new SO imposed post-authorisation and SOs re-classified

Product Name	Description of SOB scope (final)	Scope change description	Reasons for changes in scope
Diacomit	To provide further observational data to support the intrinsic anticonvulsant activity of stiripentol, and to further support its safety and efficacy in the treatment of Dravet's syndrome.	In R/11 the SO to provide results from randomised placebo controlled study was amended to "robust observational study data to support the efficacy and safety of stiripentol to control clonic seizure or tonic-clonic seizure in Dravet's Syndrome"	Difficulties in conduct of the study (consortium disbanded, slow approval process) + new PK data indicate that original study would unlikely address the research question
Intelence	TMC125IFD0000003 is a retrospective observational study which will be conducted to describe the antiretroviral activity of and resistance to etravirine in combination with background regimens containing boosted PI other than darunavir/ritonavir, using clinical cohort data of HIV 1 infected patients. Following agreement with the CHMP on the protocol, the final results for the study should be provided to the CHMP no later than 2Q 2013.	In procedure R/15 confirmatory study on the combined use of etravirine with boosted PIs other than darunavir/ritonavir was replaced with a retrospective observational study (recommended in CHMP SA)	Due to slow recruitment in the original study
Prezista	[Former SO: The final study report from the interaction study TMC114 C163 (A Phase I, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between rifabutin and DRV, co-administered with low-dose ritonavir, at steady state)]	In R/8 re-classified into a follow-up measure	In the light of otherwise accumulated evidence of efficacy and safety
Prezista	[Former SO: The week 96 final study report from study TMC114-C214 should be provided.]	Re-classified into a follow-up measure in R/8	The 96 weeks data are no longer considered relevant as a SO within the context of this MA (highly experienced patients). Data remain of relevance for expansion of present indication.

Product Name	Description of SOB scope (final)	Scope change description	Reasons for changes in scope
Prezista	[Former SO: The cut-off Q2 2007 study report from study TMC114 C208 (An open label trial of TMC114/RTV in HIV-1 infected subjects who were randomized in the trials TMC114 C201, TMC114 C207 or in sponsor selected Phase I trials) should be submitted.]	In R/8 re-classified into a follow-up measure	Results of this study are not expected to modify the outcome of the other Phase IIb studies
Tyverb	To provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO)	Revised in R/28: from dedicated randomised clinical study to evaluate the incidence of brain metastases (terminated due to lower than expected incidence of CNS metastases) to combination of data from 3 studies on incidence CNS metastases	Original study terminated due to lower than expected rate of CNS metastases
Vectibix	To submit the final clinical study report of PACCE study including the safety-efficacy analysis in relation with KRAS	Trial discontinued early (outcome communicated in SOB 004) and CHMP agreed (in SOB 014 and R/12) to remove the SOB to provide final study report (study discontinued)	No additional conclusions would be drawn from this study.
Vectibix	To complete a confirmatory trial examining panitumumab monotherapy in licensed indication. In particular to provide the clinical study report of the primary data analysis from the 20080763 study	New SO imposed in procedure R/9	Data submitted post-authorisation increased the level of uncertainty as to whether the results from the combination trials will be able to support the monotherapy indication, therefore additional SO was imposed

Product Name	Description of SOB scope (final)	Scope change description	Reasons for changes in scope
Vectibix	<p>To resolve the uncertainties about RAS testing by:</p> <ul style="list-style-type: none"> ▶ collecting information about the range of diagnostic tests conducted in clinical practice and their performance; ▶ collecting data on and evaluating the compliance of physicians with the recommended use of Vectibix in confirmed cases of wild-type tumours. 	New SO imposed in procedure R/18	New SO to address concerns about reliability of the current methods of KRAS testing and compliance of the prescribers with the recommended use of CMA product New SO to address concerns about reliability of the current methods of KRAS testing and compliance of the prescribers with the recommended use of CMA product

The majority of specific obligations did not require a change in the due date (59/83 of all currently pending and completed, and 40/57 of completed specific obligations). Slightly more than a tenth of specific obligations required an extension of the due date by more than a year.

Figure 34. Extensions of due dates for specific obligations, all specific obligations (completed or pending) (N=83)

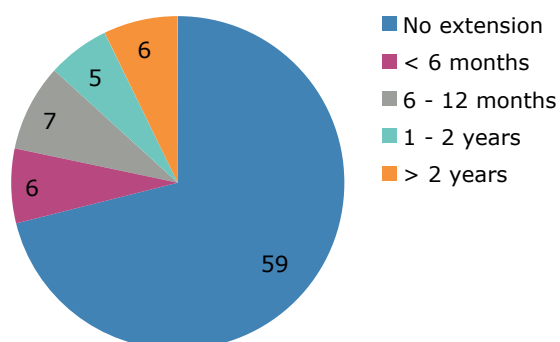


Figure 35. Extensions of due dates for specific obligations, all specific obligations completed (N=57)

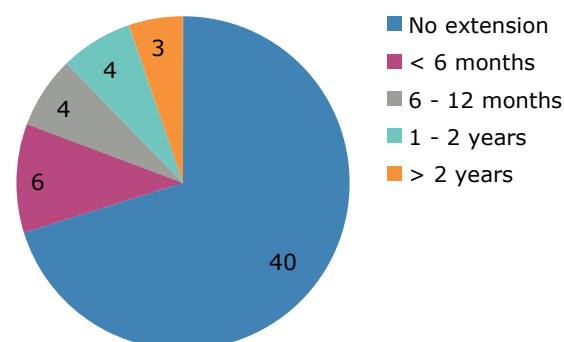
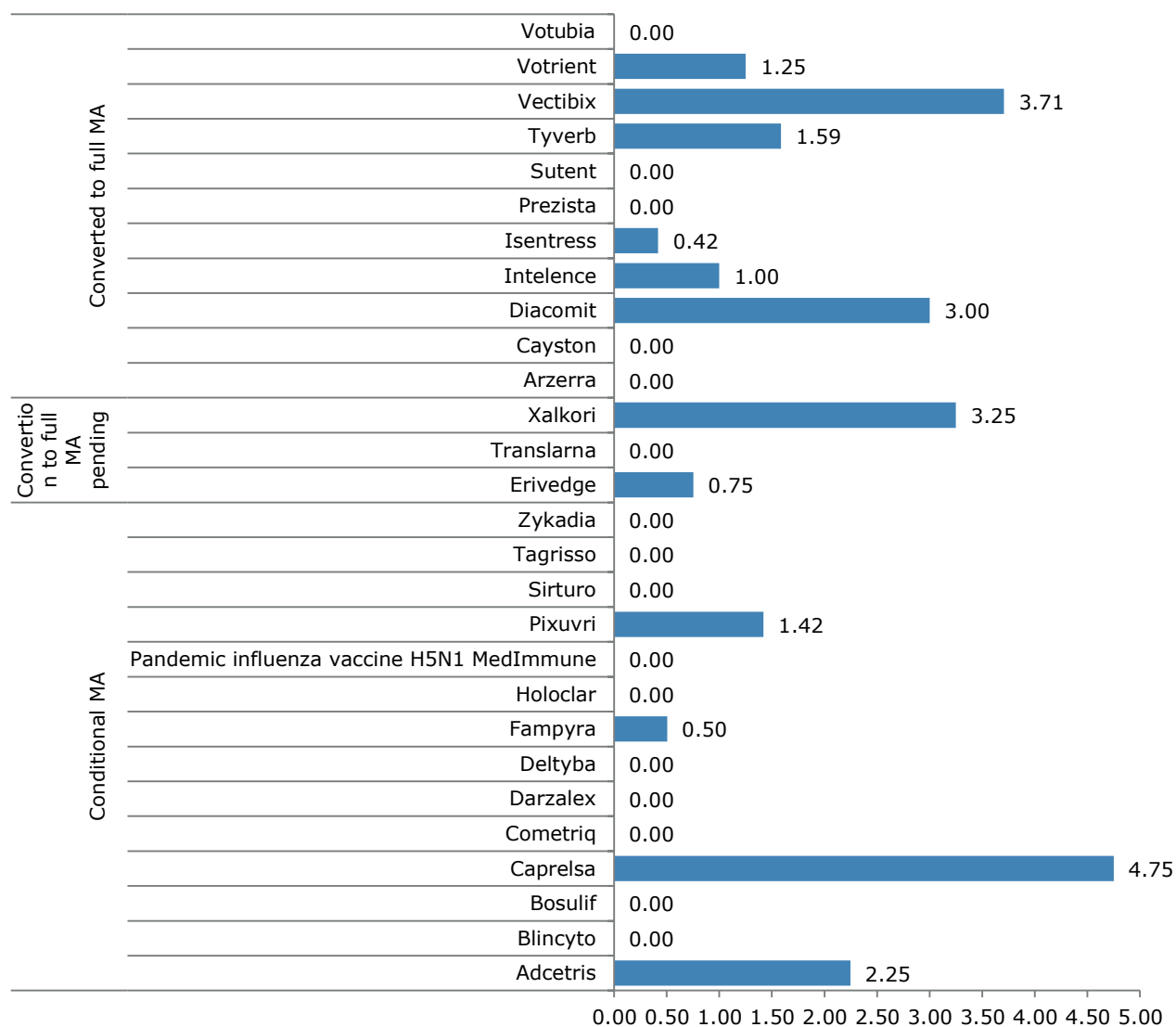


Table 5. Reasons for extensions of due date for completion of a specific obligation longer than 1 year

Product Name	Description of SO scope (final)	Extension (days)	Reasons for due date change
Adcetris	To perform a single-arm study in a similar patient population as the sALCL population investigating response rate, duration of response, rate of (second) ASCT and data in subpopulations (including but not necessarily restricted to ALK status and age) based on a CHMP agreed protocol (Study C25006).	1826	Slow recruitment. Extension granted due to 'rarity of the disease and the further limiting effects on patient availability due to the characteristics of the patient population to be studied in the context of an already registered indication'
Caprelsa	An open label trial based on a CHMP approved protocol, comparing RET negative and RET positive patients with sporadic medullary thyroid cancer treated with vandetanib. The study will include approximately 60 % of patients who receive vandetanib within the EU. [..]	1735	Slow recruitment due to difficulties in meeting the inclusion criteria
Diacomit	To provide further observational data to support the intrinsic anticonvulsant activity of stiripentol, and to further support its safety and efficacy in the treatment of Dravet's syndrome.	912	SO replaced with another study
Pixuvri	To conduct a randomised controlled Phase 3 study (PIX306) of pixantrone-rituximab vs gemcitabine-rituximab in patients with aggressive B-cell NHL, who failed front line CHOP-R who are not eligible for autologous stem cell transplant (ASCT) (2nd line) or failed ASCT (3rd or 4th line). A clinical study report should be submitted.	519	Delays in opening new sites and enrolment
Tyverb	To provide comparative data on the incidence of CNS metastases from studies EGF108919 (COMPLETE), EGF105485 (TEACH) and EGF106708 (ALTTO)	579	SO replaced with another activity
Vectibix	To provide data on Quality of Life of 20050181 study	546	Not specified

Product Name	Description of SO scope (final)	Extension (days)	Reasons for due date change
Vectibix	To submit the clinical study summary report of the SPIRITT study including the safety efficacy analysis in relation with KRAS	1188	Due to slow enrolment and due to delays in the occurrence of the relevant events necessary for the event-driven primary endpoint (PFS)
Vectibix	<p>To resolve the uncertainties about RAS testing by:</p> <ul style="list-style-type: none"> ▶ collecting information about the range of diagnostic tests conducted in clinical practice and their performance; ▶ collecting data on and evaluating the compliance of physicians with the recommended use of Vectibix in confirmed cases of wild-type tumours. 	944	Due to a delay in the launch of the studies
Votrient	Submit the study report for VEG108844 (a study of pazopanib versus sunitinib in the treatment of subjects with locally advanced and/or metastatic renal cell carcinoma). [..]	488	Due to a substantial amendment in the final analysis of the studies to increase the sample size
Votrient	Submit an updated pooled analysis of the PFS data as assessed by the Investigator from study VEG108844 and VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma—a sub study of VEG108844). The studies should be appropriately powered to demonstrate non-inferiority with a margin of 1.22 with 794 PFS events per Investigator.	457	To reach required 794 progression events based on MAH's projection
Xalkori	The MAH is requested to update OS status of study A8081007 and provide the final data within 9 months after the required 238 OS events have been reached. The CSR should also include a detailed safety analysis.	1187	In order to obtain mature OS data

Figure 36. Overall extension of due date for obtaining comprehensive data (completion of all SOs), products currently authorised (N=28)



It is interesting to note that, although sometimes the changes in scope and timelines of specific obligations were related to difficulties in recruitment and study initiation, in some cases it was linked to better-than-expected outcomes (e.g. lower than expected incidence of metastases or longer survival).

Changes to the scope and due dates of specific obligations have led to change in the final target date for availability of comprehensive data on the product (date of completion of all specific obligations). This ranged from no impact to an extension of slightly less than 5 years (Carpelsa). Detailed information on the extent of this impact is presented in the figure below.

Of the pending specific obligations for products that still have conditional MA (excluding the

SO results under assessment at the time of data cut-off for this report), more than three quarters did not have any changes to the due date and none had any major changes to the scope. This appears generally in line with what was observed with products that had already converted to full marketing authorisations, therefore the risk that analysis based of converted CMAs only would have excessively selected products with fewer challenges in meeting the specific obligations seems low.

Figure 37. Extensions of due date for specific obligations, all specific obligations currently pending (N=22)

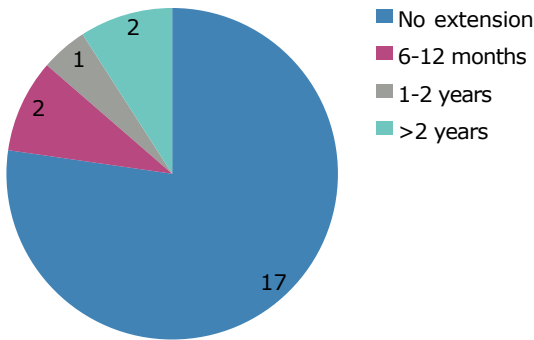
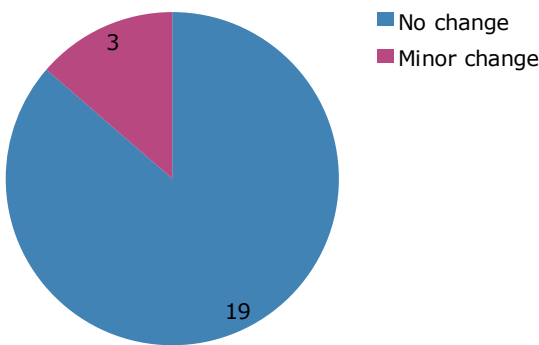
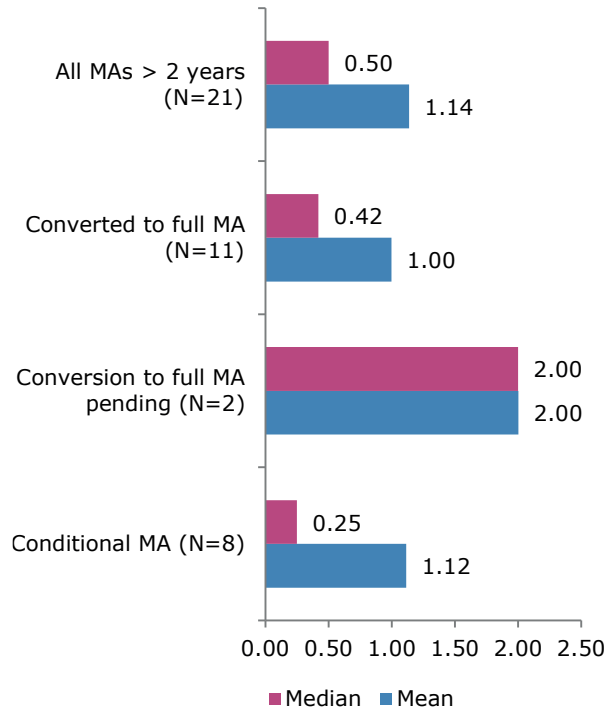


Figure 38. Changes to the scope of specific obligations, all specific obligations currently pending (N=22)



Also comparing the extensions to completion of latest specific obligation due for products, excluding those authorised within last two years (half of the historical average time to conversion to standard MA), there are no obvious differences that could not be linked to the small sample size.

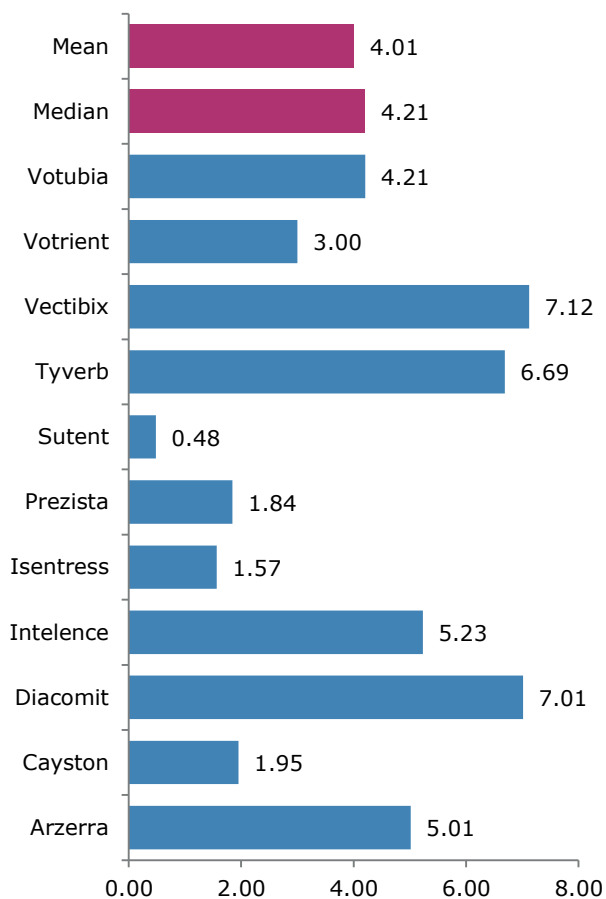
Figure 39. Average and median extension of due date by current of the application, excluding withdrawn products and products authorised within last two years (N=21)



Conversion to marketing authorisation not subject to specific obligations

For the products that have completed the specific obligations and for which a "standard"/"full" marketing authorisation has now been granted, the duration of time, for which the authorisation was conditional (i.e. time to "switch") ranged from half a year to just over seven years.

Figure 40. Time from granting CMA till conversion to standard MA in years, all CMAs converted (N=11)



For the authorisations that currently remain conditional, a third of specific obligations (11/33) has been completed (7) or the results are under assessment (4), while the remaining two thirds of specific obligations are pending.

The submission of results of specific obligations was in the majority of cases made on time. Nevertheless there have been some occasions, when the due date for completion had not

been amended in Annex II, even though the submission was delayed. Smaller delays under one month could be not considered major and in some cases can be linked to MAH's intention to synchronise the submission with EMA's assessment timetables (i.e. not having impact on the timelines of assessment of results). Longer delays were limited in numbers (4/57) and affected only two products (Diacomit and Vectibix).

In addition, there was an overall tendency over time for submissions to become earlier in relation to the due date.

Figure 41. Submission of specific obligation results in relation to the due date (N=57)

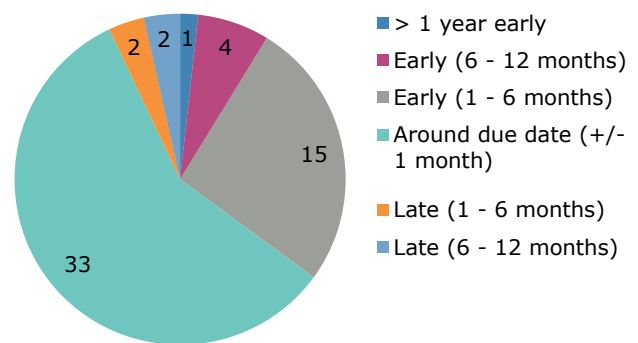
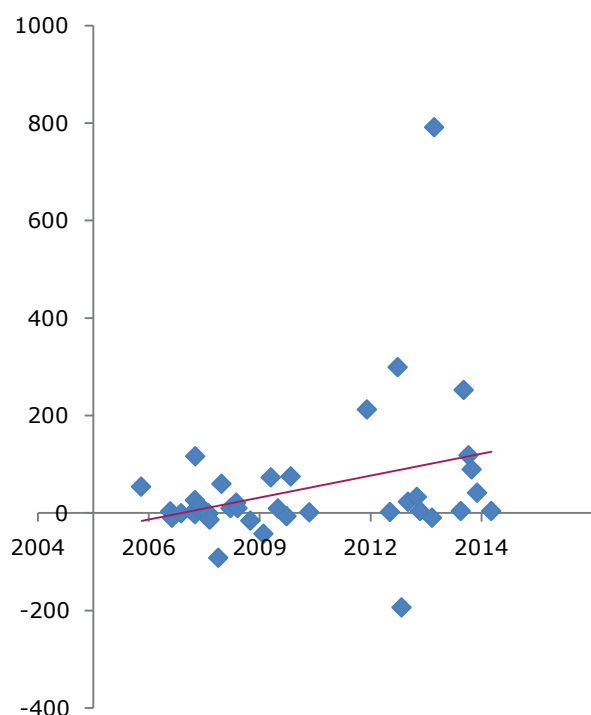


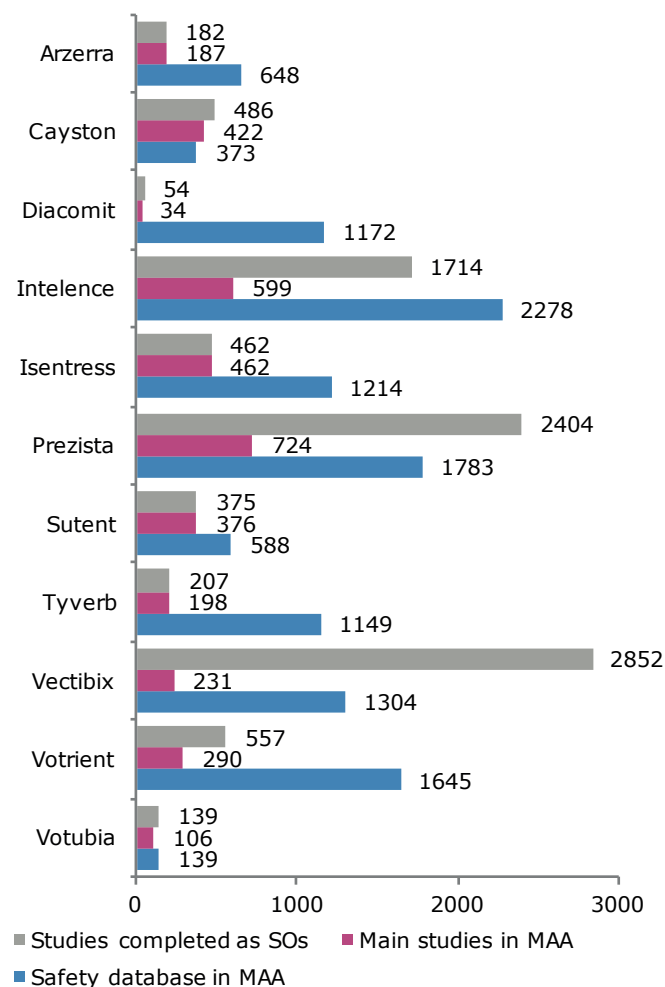
Figure 42. Accuracy of submission as number of days in advance of due date (delay = negative number), arranged by the submission date (N=57)



Data generated in specific obligations

For the products for which comprehensive data has been generated in specific obligations (i.e. products that now have a “standard” marketing authorisation), the information generated in studies conducted as specific obligations was based on at least equivalent and often larger sample size of subjects receiving the product, as compared to that in main/pivotal studies provided at the time of authorisation. These numbers, however, require caution with the interpretation, as patients included in the initial data package could be followed up as part of specific obligations (or even included in different studies in the initial data package as in the case of Cayston, where one of the main studies was continuation of another).

Figure 43. Number of subjects receiving the CMA product in main studies and safety database at the time of CMA, and in studies completed as specific obligations, all products converted to standard MA (N=11)



Most (8/11) of the products that have their specific obligations completed and obtained MA not subject to specific obligations had an extension to their indication while the authorisation was conditional. For four of these products there was an extension of the target population of the indication based on data generated in specific obligations.

Figure 44. Extensions of indication while product has CMA, all CMAs converted into “standard” MA (N=11)

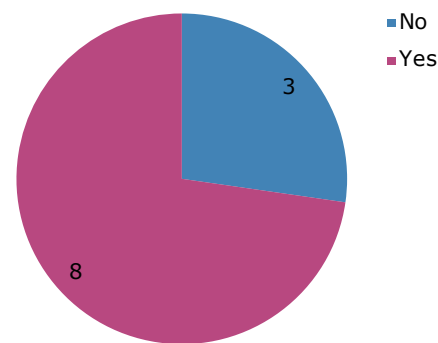
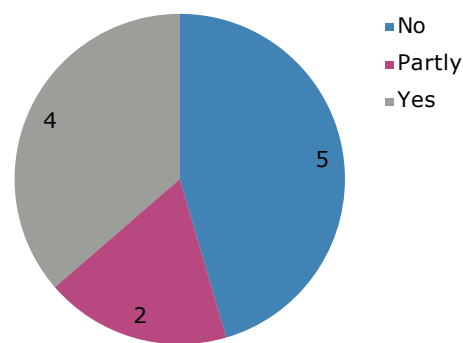


Figure 45. Changes to indication based on data generated in specific obligations, all CMAs converted into “standard” MA (N=11)



Partly = SO results affected wording of SmPC section 4.1 but did not lead to changes to the target population

The amendments to the target population of therapeutic indication that were based on data generated in specific obligations are summarised in the table below.

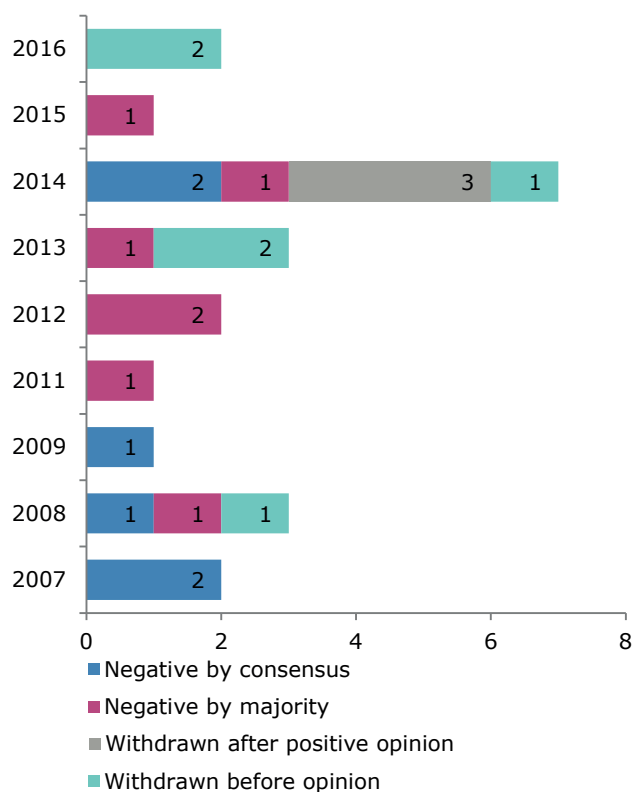
Table 6. Amendments to the therapeutic indication while authorisation conditional, former CMAs with amendments to target population of the indication based on SO data (amendments based on SO data shown in bold and red, all insertions underlined, all deletions strikethrough)

Product name	Indication after conversion to standard MA
Prezista	<p>Co-administered with 100 mg ritonavir in combination with other antiretroviral medicinal products for the treatment of HIV-1 infection in <u>treatment-experienced</u> adult patients, <u>including those that have been highly pre-treated who failed more than one regimen containing a protease inhibitor</u>. <u>Careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic or phenotypic testing (when available) and treatment history should guide the use.</u></p>
Sutent	<p>Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance treatment of advanced and/or metastatic renal cell carcinoma (MRCC) <u>after failure of interferon alfa or interleukin-2 therapy</u></p>
Vectibix	<p>Treatment of <u>adult</u> patients with wild-type KRAS <u>EGFR-expressing</u> metastatic colorectal cancer:</p> <ul style="list-style-type: none"> • <u>in first-line in combination with FOLFOX.</u> • <u>in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).</u> • as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens
Votubia	<p><u>Treatment of adult patients with renal angiomyolipoma associated with tuberous sclerosis complex who are at risk of complications (based on factors such as tumour size or presence of aneurysm, or presence of multiple or bilateral tumours) but who do not require immediate surgery. The evidence is based on analysis of change in sum of angiomyolipoma volume.</u></p> <p>Treatment of patients <u>aged 3 years and older</u> with subependymal giant cell astrocytoma associated with tuberous sclerosis complex who require therapeutic intervention but are not amenable to surgery.</p> <p>The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated</p>

Unsuccessful conditional marketing authorisations

In order to provide a more comprehensive picture of conditional marketing authorisations, also “unsuccessful” conditional marketing authorisations have been analysed. This analysis included all applications that had either concluded with a negative CHMP opinion or have been withdrawn by the applicant (provided, that the procedure has had at least one assessment phase concluded by the CHMP before that), and where a possibility of a conditional marketing authorisations was discussed in the final (or latest) CHMP assessment report.

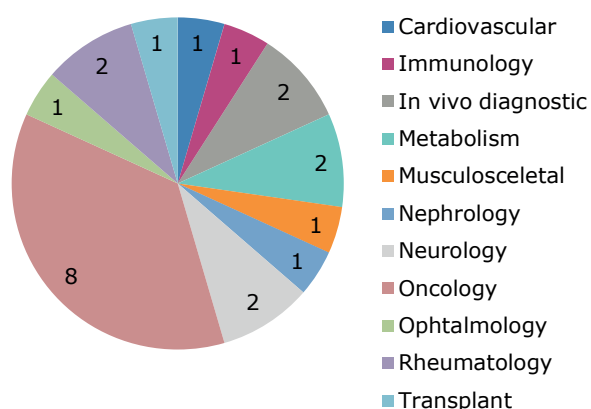
Figure 46. Unsuccessful CMAs by outcome type per year (N=22)



Aside from a peak in 2014, which was partly driven by three inter-related applications (for use in combination) that were withdrawn after positive CHMP opinion due to late breaking findings in ongoing clinical studies, there was

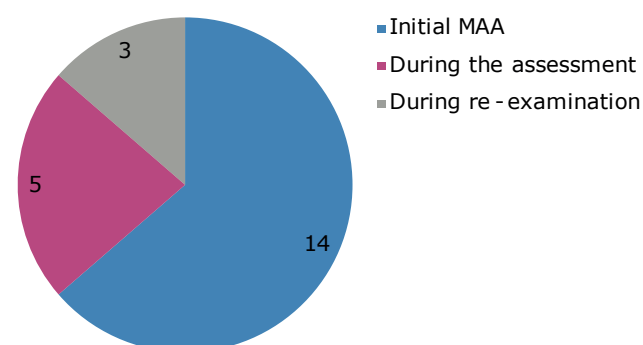
no particular trend of increase or decrease of “unsuccessful” CMA applications. Notably, even though the total number of “unsuccessful” applications was lower than CMA’s granted (22 vs. 30), they represented a wider variety of different therapeutic areas. Nevertheless, oncology was still the largest represented area.

Figure 47. Unsuccessful CMAs by therapeutic area (N=22)



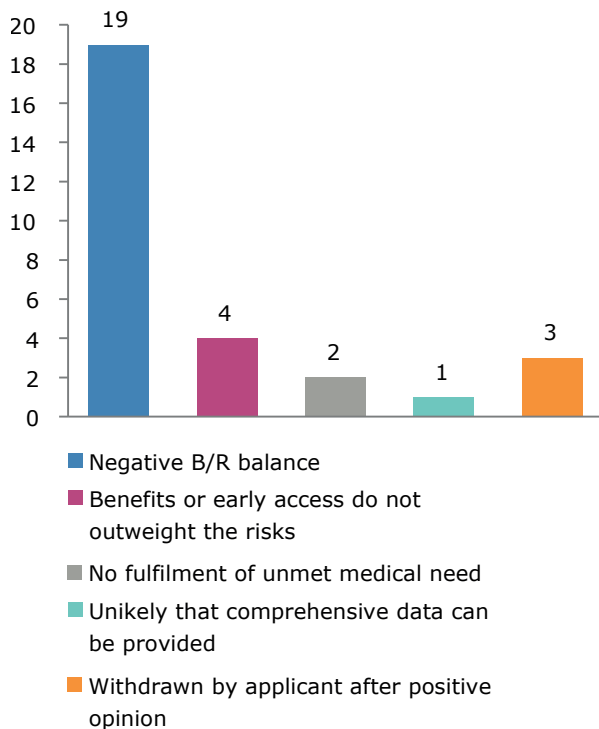
Almost three quarters of “unsuccessful” CMA applications (16/22) had orphan designations. A higher proportion (14/22) of such applications contained the proposal for conditional marketing authorisation already in the initial application.

Figure 48. Unsuccessful CMAs by stage of procedure when CMA was first considered (N=22)



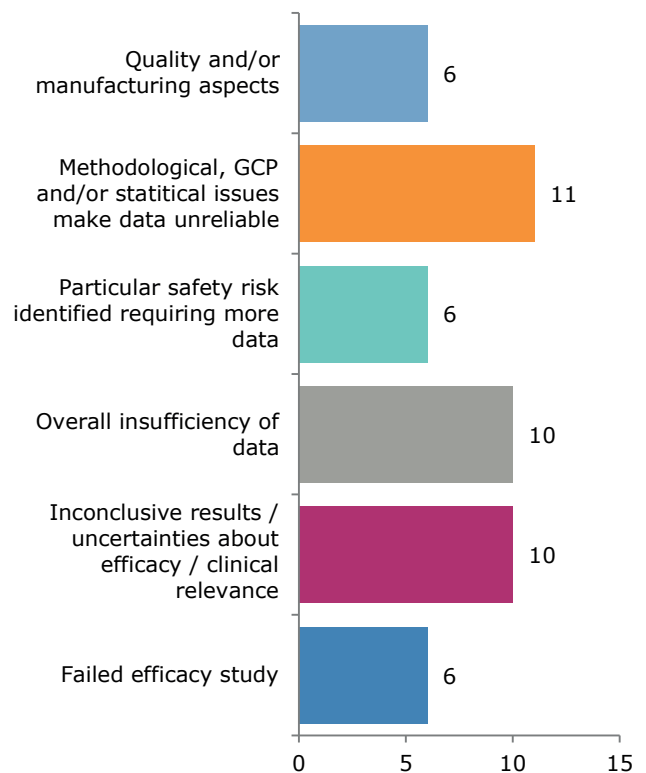
Regarding the criteria for granting conditional marketing authorisation, in almost all cases (19/22, except three cases of withdrawal following a positive CHMP opinion discussed above) the lack of a positive benefit–risk balance was the reason for a negative outcome, only in some cases supported by references to other criteria not being met.

Figure 49. Conditional MA requirements not met in unsuccessful CMAs, as reflected in CHMP reports (N=22)



The reasons in the argumentation substantiating conclusions on negative benefit risk balance were categorised in several groups, but none stood out as most common.

Figure 50. Types of issues at the basis of CHMP’s conclusions on negative benefit–risk balance (N=19)



Interestingly, a very strong majority (20/22) of unsuccessful CMAs had previously received scientific advice. However, the adherence to the SA, in terms of primary endpoint, comparator(S) and statistical methods, was lower than for products that received a CMA. A development programme not adherent to received scientific advice was more likely to fail to receive a CMA, while an adherent development more likely to result in a CMA being granted (see the table below).

Figure 51. Adherence to SA/PA in the MAA submission, all CMAs with SA/PA (N=20)

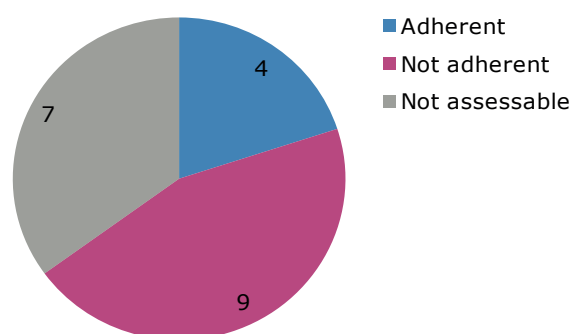


Table 7. Adherence to SA/PA and outcome of the MAA procedure, successful and failed products with SA/PA, where adherence could be assessed (N=29)

Adherence to SA/PA	CMA granted	MA not granted
Adherent (N=14)	10 (71.4%)	4 (28.6 %)
Non adherent (N=15)	6 (40%)	9 (60 %)

Late breaking information

By the end of 2016 further six medicinal products were recommended by the CHMP for conditional marketing authorisation – Alecensa, Lartruvo, Ninlaro, Ocaliva, Venclyxto and Zalmoxis. As these products were not authorised at the time of data lock for this report, they are not included in the data presented.

At the CHMP meeting in November 2016 within the annual renewal procedure for Translarna, having assessed the submitted results of the outstanding specific obligation, the CHMP concluded that although the imposed study had been conducted it had not led to comprehensive clinical data confirming the positive benefit- risk balance in the concerned indication and therefore recommended

imposition of a new specific obligation in order to generate further clinical data.

Following completion of specific obligations, marketing authorisations not subject to specific obligations were granted on 11 November 2016 for Xalkori and on 14 November 2016 for Erivedge.

Discussion and conclusions

Since introduction of the conditional marketing authorisation route there has been considerable interest among stakeholders, even if it remains just a small fraction of authorisations granted. However, there also appears to be certain reluctance of applicants to request this authorisation type upfront in the submission for the marketing authorisation. The CHMP, however have actively used this tool and considered its application when appropriate, as demonstrated by numerous cases when conditional marketing authorisation was eventually recommended, even though it was not proposed by the applicant in initial submission.

Granting conditional marketing authorisation, as foreseen, is based on less comprehensive data. However in half of the cases at the time of granting initial authorisation data from at least one phase III study formed part of main evidence. The main/pivotal studies used for initial authorisation most often were open label (57%), randomised (59%) studies measuring a pre-defined response rate as primary efficacy endpoint (53%). In some respects differences were seen between the therapeutic areas, e.g. for oncology products it was more common to have single arm studies (52% of studies). Open label studies were more common in oncology (76%) and infectious diseases (43%), where more "objective" endpoints (laboratory test results or independent assessment of radiology results) are mostly used. On the other hand, in neurology area, where more patient or observer dependent endpoints are applied, all studies were blinded.

Imposed specific obligations have mostly been clinical studies of various development phases. Over time, the extent of specific obligations has become more focused, requesting final results from one or few clinical studies. Although often the imposed clinical studies were focused on endpoints different from the primary endpoints of main/pivotal studies at the time of initial

authorisation (much more rarely relying on response rate), it was also relatively common to request further data based on same or similar endpoints. The duration of treatment and follow-up in studies imposed as specific obligations was clearly longer than for the information available from main/pivotal studies at the time of authorisation, and the number of subjects receiving the product as part of imposed studies was often, but not necessary, higher.

In most cases the studies imposed as specific obligations generated data in patients within the indication granted, but in some cases data in closely related patient populations also contributed to the generation of comprehensive data in support of the granted indication. In about a third of cases the data from specific obligations led to a change in the definition of target population in the therapeutic indication.

Although half of the products did not have any results from a phase III study at the time of authorisation, and many of the imposed studies were not traditional phase III confirmatory studies, only two CMA products were not expected to provide phase III or IV study results either as part of initial authorisation or specific obligations – of these one product did not have the study phase specified, and the second one had to complete post-authorisation a phase II study in almost 8-times larger study population. The totality of data provided for initial authorisation and imposed as specific obligations for a product almost always included comparative data versus active control or placebo/ background therapy. Apart from some products mainly in oncology area, it also included blinded study data.

A very limited number of specific obligations required major changes to their scope (<5%), indicating that the initially requested type and amount of data to be generated post-

authorisation as part of specific obligations are generally maintained.

Limited number of specific obligations required extensions of the due date by more than one year (<15%). Although such changes can be driven by difficulties in the conduct of the study, in some cases they were required due to better than expected results and in all cases formal extensions were substantiated with a justification supported by the CHMP. In addition, extensions of due date post-authorisation in general could reflect a thorough approach by the CHMP at the time of initial authorisation, agreeing only to strict timelines initially and allowing more flexibility only if the applicants come with an appropriate justification. Also, although uncertainties related to data not yet available should be limited in time, an earlier authorisation also extends the public health and patient benefits stemming from earlier access in cases when the positive benefit-risk balance is eventually confirmed (which so far has been the case for all conditionally authorised products).

Submission of specific obligations results was often done in advance of the imposed due date and only very few submissions were delayed. Compliance in terms of study conduct can be considered generally acceptable, since new studies were only imposed rarely and based on new results, not driven by non-compliance. Overall, the modifications of specific obligations agreed and compliance can be considered acceptable.

In case of unsuccessful CMAs it was rarer to consider CMA for first time 'late' in the procedure than it was for successful CMAs. It could be speculated that this might be due to selection bias (since products with CMA request in the initial application will always have CMA discussed in the CHMP reports, while at later stages CMA could be considered "informally" without making a formal proposal if application is already expected to be unsuccessful).

It is noted that products that followed scientific advice were more likely to obtain the CMA, while products that did not were more likely not to obtain an MA.

The number of therapeutic areas where products have managed to obtain conditional marketing authorisations appears limited, and it could be encouraged to continue exploring if this authorisation route can be used in other areas with seriously debilitating and life threatening conditions (so far mostly unsuccessful), in order to bring the authorisation of new products earlier, whenever appropriate. In this respect identification of appropriate intermediate endpoints could provide sufficient reassurance required for the initial authorisation.

It has been recognised that conditional marketing authorisation is an important tool for ensuring timely access to medicines in areas of unmet medical need. For the products that have already completed the specific obligations, the granting of CMA provided regulatory approval on average 4 years earlier, as compared to when a standard marketing authorisation could be granted.

Improved early dialogue and prospective planning of CMAs could support prompt assessment of such applications, as well as ensure that the post-authorisation activities have been planned carefully and timely, facilitating rapid completion of additional studies and availability of comprehensive data. Involving other stakeholders in this process (in particular Health Technology Assessment Bodies) aims at facilitating timely completion of other activities required for access to medicines for patients. An analysis of reimbursement decisions for conditionally authorised medicines in oncology has been reported in the literature⁸. Some delays have been observed the timelines for reaching a positive HTA recommendation are clearly shorter than the average time required to generate comprehensive data for a "standard" authorisation.

⁸ Early market access of cancer drugs in the EU. Martinhalbo J et al. *Annals of Oncology* 27: 96–105, 2016

Annexes

Annex 1

[Detailed information on conditional marketing authorisation](#)

Annex 2

[Detailed information on unsuccessful CMAs](#)



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Conditional marketing authorisation
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