Marketing authorisations for unmet medical needs: a critical appraisal of regulatory pathways in the European Union

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ABSTRACT

For unmet medical needs, the European Union has established fast-track regulatory pathways for ensuring patients' access to essential treatments. It is the case of Conditional Marketing Authorisation (CMA) and the Authorisation under "Exceptional Circumstances" (EXC), which can be granted even if the clinical part of a medicinal product's dossier is not yet complete. The article aims to discuss the peculiarity of such regulatory pathways and assess the impact of their application on products' market access and penetration. A review of the regulatory history of medicines authorised with EXC or CMA has been performed on European Institutional databases (e.g., EMA portal, Union Register). Excluding vaccines, 71 CMAs and 51 EXCs were granted in the EU from 2002 and 2006, respectively, to 2022. Most CMAs have been released for the treatment of different types of tumours, while most of EXCs for alimentary tract and metabolism diseases, especially in the paediatric population, addressing unmet medical needs. Therefore, both regulatory pathways are effective for placing on the market essential medicines, preserving the initial positive benefit-risk balance. However, on average, CMAs are converted into standard authorisations only after a time which is significantly longer than the provided one-year renewal period, suggesting that such a regulatory pathway is still far from optimized.

Keywords (max 6)

Conditional marketing authorisation, Exceptional circumstances, Unmet medical needs, Regulatory Science.

1 Introduction

Industrial medicinal products intended to be marketed in the European Union must, in general, obtain a preventive Marketing Authorisation (MA), issued after a positive opinion by the competent Authority (CA) about its benefit/risk balance. The opinion is based on the evaluation of a dossier submitted by the Applicant, reporting comprehensive quality, nonclinical and clinical data about the medicinal product, to demonstrate its quality, safety, and efficacy. However, the timely placing on the market of satisfactory methods for diagnosis, prevention or treatment is crucial to meet the clinical needs of patients affected by rare or life-threatening diseases, or to respond to emergency situations, such as pandemic outbreaks. In such cases, conventional regulatory pathways to the MA may not be appropriate, due to the fast rate of spread and severity of the disease (e.g., COVID-19 pandemic) or the difficulty, owing to the rarity of the pathology, to enrol enough patients in clinical trials to provide robust clinical evidence. In these contexts, a new equilibrium should be reached between regulatory standards and the need to ensure timely patients' access to essential treatments.

For this reason, the European legislator, on the one hand, has developed tools that allow early access to medicines or a faster route to the MA, but do not represent a separate MA pathway, like compassionate use (EMA, 2023b), PRIME Program (EMA, 2023e), accelerated assessment (EMA, 2023c) and rolling review (Roelie, 2022). On the other hand, it has introduced two proper regulatory pathways not only aimed at facilitating the obtainment of the MA for medicinal products addressing unmet medical needs, in the interest of public health, but also yielding actual MAs, namely the Conditional Marketing Authorisation (CMA) and the Authorisation under "Exceptional Circumstances" (EXC).

The EXC, ruled by Regulation (EU) No. 726/2004 and Directive 2001/83/CE, provides a route for medicinal products to be authorised when clinical data are not complete, and it is granted in cases where full clinical data cannot be obtained for objective and verifiable reasons.

The CMA, ruled by Regulation (EU) No. 726/2004 and by Commission Regulation No. 507/2006 provides, under certain conditions and by fulfilling specific requirements, a regulatory path through which medicines can be authorised although some clinical – and, in emergency cases, also nonclinical and quality - data might not be provided completely at the time of submission of the dossier. It is expected that the benefit-risk balance of the medicinal product is positive at the time of assessment, and that the applicant complies with all obligations within the times and in the ways established by the European Medicines Agency (EMA), under penalty of withdrawal of the product from the market. Differently from the EXC, the CMA is not meant to remain conditional indefinitely, but it is to be converted into a non-conditional authorisation as soon as comprehensive clinical data are available.

The article aims at assessing the success of the CMA and the EXC in both improving patients' access to treatments and facilitating the obtainment of the MA. In this light, the regulatory history of EXCs and CMAs granted by the Union from 2002 and 2006, respectively, to 2022, have been reviewed, determining the percentage of them converted to standard MA, the average time, the number of extensions of therapeutic indications pre and post conversion and the number of withdrawn medicines.

2 Regulatory overview

For a medicinal product to access the regulatory tools to facilitate the obtainment of the MA here considered, namely the CMA and EXC, some common requirements exist, such as the unmet medical need and the seriousness of the disease. However, the choice between one or the other authorisation route depends on additional requisites. A summary of the CMAs and EXCs features is shown in **Table 1**.

2.1 Conditional Marketing Authorisation

The CMA is regulated under Regulation (EC) No 726/2004 (European Parliament and Council, 2004), as amended by Commission Regulation (EC) No. 507/2006 which provides procedures, requirements, and categories of eligible medicinal products (European Commission, 2006). The latter entered in force on 2nd April 2006. The Regulation (EC) No 726/2004 was furtherly amended by Regulation (EU) No 5/2019 (European Parliament and Council, 2019)

In a CMA, the Authorisation is issued prior to the submission of comprehensive clinical data. A CMA may be granted if a medicine aims at the treatment, prevention, or medical diagnosis of seriously debilitating or life-threatening diseases in case of unmet medical needs, i.e., conditions for which satisfactory methods of diagnosis, prevention or treatment authorised in the Union do not exist, or - even if such methods exist - new medicinal products will be of major therapeutic advantage (European Commission, 2006). Moreover, the CMA can also be used in response to emergency situations connected to public health threats declared by the Word Health Organisation or by the Union, or in the case of orphan medicinal products.

In general, comprehensive non-clinical and quality data should be made available by the applicant at the time of dossier submission, while clinical data may be partial or missing. The available data may be even more limited in the cases of products intended to be authorised and used in emergency situations. In any case, the data provided should be sufficient to allow EMA assessing the benefit risk balance of the novel treatment.

The benefits to public health of the immediate availability on the market of the product should outweigh the risk inherent to the fact that additional data are still required (art. 4, Reg. 507/2006). However, a positive assessment does not exempt the applicant from providing full clinical data in the post-marketing phase. Indeed, CMA holders are subject to certain specific post-marketing obligations imposed and annually renewed by the EMA. The list of these obligations is publicly available, on the EMA website, through documents such as the European Public Assessment Report (EPAR) and Summary of Products Characteristics (SmPC). The marketing authorisation holder (MAH) is required, in the established timeframe, to complete ongoing studies or conduct new studies, according to the requested obligations. In case of non-compliance, the European Commission may decide to vary, suspend, or revoke the MA.

The CMA is valid for one year and it may be renewed annually. At least six months before expiry, the MAH should apply for a renewal and submit to the EMA an interim report on the fulfilment of the specific obligations. However, the conditional MA is intended to be switched into a non-conditional MA. Indeed, upon MAH's request, a medicinal product initially authorised with a CMA may be granted a standard authorisation valid for 5 years, renewable, after the fulfilment of all specific obligations and a positive opinion by the EMA.

2.2 Authorisation under "exceptional circumstances"

EXC has been introduced into the European regulatory framework, before the CMA, with Council Regulation (EEC) No 2309/93, together with the institution of the European Agency for the Evaluation of Medicinal Products (now EMA). Regulation (EEC) No 2309/93 entered in force on 1st January 1995 and was repealed in 2005. The EXC, now regulated by Regulation (EU) No 726/2004, art. 14(8) and Directive 2001/83/EC, art. 22, may be granted only when the applicant can demonstrate that comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use cannot be provided for objective, verifiable reasons, such as the rarity of the therapeutic indications for which the product is intended or scientific or ethical reasons (Annex I, point 6, Dir. 2001/83/EC). The EXC may be granted subject to certain specific post-marketing obligations, and it is not intended to become a "normal" MA, as the applicant, by the very nature of the EXC, is not expected to be able to provide full comprehensive data. Differently from the CMA, the EXC is valid for 5 years, renewable, although the conditions for renewal are subject to an annual reassessment.

3 Material and Methods

For CMAs, analysis focuses on the period from 2nd April 2006 (Data of coming into effect of the Regulation (EC) No 507/2006) to 30th November 2022; For EXCs, it focuses on the period from 1st January 2002 to 30th November 2022. Indeed, although the EXC existed before 2002, regulatory

documents publicly available on the institutional portals frequently lacks relevant information on the regulatory procedural steps to grant the MA up to 2002.

The main source for data about the regulatory history of the medicinal products under analysis is the EMA official website (https://www.ema.europa.eu/en). Search keywords: “conditional marketing authorisation” (search bar), “exceptional circumstances authorisation” (search bar), “human” (flag in search filter) and “EPAR” (flag in search filter). Records accompanied by the letter “C" for conditional or “E” for exceptional circumstances were considered. Among these, vaccines were excluded from the analysis.

For each medicinal product, the following documents has been analysed: EPAR-Product Information, EPAR-Public Assessment Report of the initial MA (or EPAR-scientific discussion), EPAR-Assessment Report for changes after the first MA, EPAR - Procedural steps taken and scientific information after authorisation and Orphan Designation Report (if available).

As confirmation in case of discrepancies between documents on dates of submission of the dossier and/or authorisation the Official European Commission Decision on the website of the “Public Health - Union Register of medicinal products” has been consulted (European Commission, 2022b). The latter has also been used to check both withdrawn and refused authorisations.

To confirm their status, orphan drugs have been searched in the “Community Register of orphan medicinal products” (European Commission, 2022a). For paediatric medicines, the European Network of Excellence for Paediatric Research’s website was used (TEDDY Network, 2022).

ATC codes have been detected from SPCs and have been confirmed by searching them in the WHO Collaborating Centre for Drug Statistics Methodology’s website (WHO Collaborating Centre for Drug Statistics Methodology, 2022). Discrepancies between ATC codes in SPCs and those on the WHOCC website have been detected and solved by considering only the latter.

4 Results

4.1 Overview of results for the Conditional Marketing Authorisation

The First CMA was granted by EMA on 1st July 2006. Since the full application of the CMA in 2006 to November 2022, there have been 107 applications and a CMA have been issued for 80 of them (nearly 75%). In our analysis we have excluded 9 CMAs released for vaccines. Consequently 71 CMAs, four of which [Zalmoxis® (allogenic T cells), Zynteglo® (autologous CD34+ cell), Lartruvo® (olaratumab) and Arzerra® (Ofatumumab)] subsequently withdrawn, have been analysed (**Figure 1**). Compared with all MAs granted in the same period, medicinal products marketed with a CMA represent almost the 6%, Sutent® (sunitinib) being the first (July 2006) and Roctavian®

(valoctocogene roxaparvovec) the last (24th August 2022). In recent years, there has been an increase in the number of CMAs granted: 27 released in the decade 2006-2016 (1st July 2006 to 30th June 2016) and 44 in the subsequent 6 years (1st July 2016 to 30th November 2022). The highest number of CMAs (11) was issued in 2020, followed by 10 in 2021 (**Figure 2)**.

It is noteworthy that 8 of 71 CMAs were issued for Advanced Therapy Medicinal Products (ATMPs). Two of them were withdrawn in the last years (Zalmoxis® and Zynteglo®). Moreover, 18 approved medicines contain monoclonal antibodies and 7 of them switched into "normal" MAs, including Arzerra® which was withdrawn later.

Of the 71 medicinal products considered, 29 (41%) were authorised for the treatment of seriously debilitating or life-threatening diseases, 3 (4%) by virtue of their designation as orphan medicinal products and 39 (55%), including withdrawals (Zalmoxis®, Zynteglo®, Lartruvo and Arzerra®), for both reasons. Twenty medicinal products (28%) have been authorised for use in the paediatric population, mostly for the treatment of different types of tumours.

Before granting a CMA, the Committee for Medicinal Products for Human Use (CHMP) has to consider if the product fulfils an unmet medical need, which the applicant should demonstrate during the application, along with justifying the necessity to introduce a new product as either there are no satisfactory ones, or a major improvement over the existing one is needed. The latter may be a meaningful improvement in efficacy or clinical safety, such as a positive impact on either the onset and duration or the morbidity or mortality of the disease. The advantages should be demonstrated over existing methods used in clinical practice, if any, using randomised controlled trials (EMA, 2016c). Based on the assessment reports of the initial MAs and on EMA's report on ten years of CMA (EMA, 2017), 5 categories of medical needs may be detected, as shown (n=67, withdrawals not considered). Most medicines have been authorised since there were no approved available therapies (38/67). Some medicines since they contributed to improve treatment effect and/or safety compared to available therapies (21/67). A small number has been approved after demonstrating improved evidence on efficacy (7/67) and an ability to select patients that will respond to therapies (1/67).

With regards to the regulatory history "pre-authorization", it is worth noting that the CMA application did not always represent the first choice for applicants. Indeed, in 22 of 68 products (n= 68, Zynteglo®, Zalmoxis® and Lartruvo® not considered), the MAHs had submitted a non-conditional MA application, which became a CMA application on CHMP's advice. Of these 22 medicinal products, 11 had completed phase III clinical trials before submitting the application and 2 had ongoing trials. Clinical data were absent for 9 products.

After the first authorization, the CMAs were switched into non-conditional MAs in 33 cases. The incidence of switching depends on the availability of phase III studies at the time of the first submission (**Table 2**), being lower for products with ongoing phase III trials and higher for products with completed or absent phase III trials.

4.2 Overview of results for the Authorisation in "exceptional circumstances"

From January 2002 to November 2022, 65 applications for EXC have been submitted, 62 of which have been approved and, consequently, granted a MA. Excluding 11 EXCs released for vaccines, 51 authorisations have been analysed (**Figure 1**). Trisenox® (arsenic trioxide) (European Commission, 2002) has been the first medicinal product to be granted an EXC on March 2002, whilst Nulibry® (fosdenopterin hydrobromide dihydrate) (European Commission, 2022c), authorised in September 2022, has been the last.

Between 2002 and 2005, 13 medicines obtained an EXC (3.8% of the overall centralized MAs issued in the same period); between 2006 and 2022, the same period considered for the CMA, 38 EXC have been issued (3.2% of the overall centralized MAs), a little more than half of the CMAs released in the same time frame (**Figure 2**). Thirty-three medicines out of 51 (65%) are indicated for paediatric population, more than double that of those with CMAs (20/71, 28%).

4.3 Grouping by Anatomical Therapeutic Chemical code

A subdivision according to the Anatomical Therapeutic Chemical (ATC) code of medicines authorised with EXC or CMA is shown in **Figure 3**. Withdrawn medicines and those with no assigned ATC code were excluded from the analysis. In total, CMAs and EXC medicines having an ATC code are 63 and 51, respectively. Among the 63 CMA medicines with an ATC code, 42 are antineoplastic agents (ATC: L01) used to treat different tumours and belong to the categories of protein kinase inhibitors and monoclonal antibodies; 8 are antivirals for systemic use and antimycobacterial drugs. Among the 51 EXC medicines, 16 are classified with an ATC code for alimentary tract and metabolism; 10 are antineoplastic agents. For all the other ATC codes there is equal or less than five medicinal products authorised.

4.4 Grouping by technology used for development

The medicinal products under analysis, which are under the centralised procedure, have been subdivided according to Annex I of Regulation 726/2004: medicinal products produced by a biotechnological process; advanced therapy medicinal products, as defined in Regulation 1394/2007 (European Parliament and Council, 2007); medicinal products containing a new active substance (i.e. not authorised in the EU until 2004) for acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions and viral diseases.

Focusing on the CMA, most of active substances (almost 60%) are small molecules and only one medicine [i.e., Waylivra® (volanesorsen)] contains an antisense oligonucleotide. Among the others, 18 are monoclonal antibodies (mAbs). The first CMA for a mAb-based product was issued in 2007, and, from 2015 till 2022, every year, at least one mAb has been authorised. Moreover, two medicinal products contain proteins or peptides obtained by recombinant DNA technology [i.e., Idefirix® (imlifidase), Natpar® (parathyroid hormone)]. Finally, the first CMA for an ATMP was released in 2015 for Holoclar® (autologous human corneal epithelial cells) and after it, almost every year, an ATMP has been authorised. In particular, the first CAR-T (Chimeric Antigenic Receptor T-cell therapies) with a CMA was authorised in 2020 and other two in the following years.

Focusing on the EXC, 15 out of 51 products authorised were produced by recombinant DNA technology, and 5 monoclonal antibodies were authorised. In total, about 39% of EXCs have been released for medicines manufactured by means of biotechnological processes. The first ATMP approved in Europe was Glybera® (alipogene tiparvovec), a gene therapy for the treatment of the familial lipoprotein lipase (LPL) deficiency, which granted an EXC in 2012 and has been withdrawn by the MAH in 2017. The other ATMP that obtained an EXC is Upstaza® (eladocagene exuparvovec), authorised in 2022. The remaining 57% of MPs is made of small molecules.

4.5 Withdrawn authorisations

Since 2002, 7 EXCs (13.7%), and 3 CMAs products (4.2%) were withdrawn. In addition, a medicinal product first approved with a CMA and later switched to non-conditional MA was withdrawn after switching. It is noteworthy that such withdrawal percentages are lower than that of medicines authorized by the EMA following the standard centralized procedure (16.3%) between 2002-2022 (EMA, 2023f). In most cases, the withdrawal was due to commercial reasons [CMAs: Zalmoxis® (EMA, 2019d), Zynteglo® (EMA, 2022), Arzerra® (EMA, 2019b); EXCs: Kolbam® (cholic acid) (EMA, 2020), aTryn® (antithrombin alfa) (EMA, 2019c), Rilonacept Regeneron® (rilonacept) (EMA, 2012a), Lumoxiti® (moxetumomab pasudotox) (EMA, 2021)], whereas a lack of efficacy was

documented only in two cases [CMA: Lartruvo® (EMA, 2019a); EXC: Xigris® (drotrecogin alfa) (EMA, 2012b)]. Finally, the marketing authorization of one product was not renewed by the MAH (EXC: Glybera®), while the obligations were not fulfilled by the applicant in another one [EXC: Onsenal® (celecoxib) (EMA, 2011b)]. Focusing on the two medicines that have been withdrawn for efficacy issues, it is noteworthy that the benefit/risk balance of both products was reconsidered after the availability of results from additional clinical trials with respect to those submitted to the first MA application.

Lartruvo® contains the monoclonal antibody olaratumab as active substance (EMA, 2019a). It is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma (STS) who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin. In 2016 a CMA for Lartruvo was granted based on a single open-label, randomised phase Ib/II clinical trial which resulted in an improvement in progression-free survival (PFS) and overall survival (OS). To confirm the efficacy and safety of olaratumab, the MAH was required to submit, by January 2020, the clinical study report of a phase III randomised double-blind confirmatory study comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic soft tissue sarcoma (ANNOUNCE study; Tap, 2020). In January 2019, the MAH communicated to the EMA preliminary results of the study. In total, 509 patients were randomised to treatment either with Lartruvo plus doxorubicin (followed by Lartruvo monotherapy until progression) or with placebo plus doxorubicin (followed by placebo monotherapy until progression). The primary endpoint for ANNOUNCE study was OS in the ITT (intention-to-treat) population and in the LMS (leiomyosarcoma) population. The secondary endpoint for ANNOUNCE study was PFS, ORR (objective response rate) and DCR (Disease control rate) in the ITT population and in the LMS population. The study gave rise to concerns about lack of efficacy because it did not meet the primary objective to prolong survival in the overall population or in the leiomyosarcoma sub-population in comparison to control (Tap, 2020). Furthermore, there was no clinical benefit in key secondary efficacy endpoints as well. Even though no safety concerns arose during ANNOUNCE study, the benefit-risk balance of Lartruvo was reviewed in negative due to the lack of superiority with respect of control. For this reason, in April 2019, CHMP recommended a revocation of the CMA previously granted for Lartruvo (EMA, 2019a).

On the contrary, Xigris® is based on drotrecogin alfa (activated), a recombinant version of the endogenous activated Protein C and produced by genetic engineering from an established human cell line (EMA, 2012b). It is used for adult patients with severe sepsis with multiple organ failure when added to best standard care. The first EXC was granted in 2002 and was valid for 5 years. In 2007 it

was renewed for further 5 years, but MAH was requested still to perform more in-depth investigation to provide data for the benefit-risk assessment of Xigris. A new placebo-controlled clinical study (PROWESS-SHOCK study; Ranieri, 2012) was conducted to confirm positive benefit/risk balance. However, the trial's results failed to meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients treated with Xigris compared with placebo (Ranieri, 2012). The study also failed its secondary endpoint of a reduction of mortality in the population of patients with severe protein C deficiency. Consequently, in 2011, the MAH requested a withdrawal of the product from the market due to lack of efficacy (EMA, 2012b).

4.6 Converted authorisation

From 2006 to 2022, 33/71 (46.5%) CMAs have been converted into standard MAs and, exception made for Arzerra®, they are still valid today. All CMAs issued from 2006 to 2013 and in the year 2018 have switched, while not all CMAs from other years have. On average, a CMA took 4.0 years to be converted into a "normal" MA, with a median of 3.0 years (IQR: 1.9-5.8 years).

Sutent® (sunitinib), Alecensa® (alectinib hydrochloride), and Darzalex® (daratumumab) switched to a standard MA in less than one year. In the initial Marketing Authorisation Assessment of Sutent® (EMA, 2006), the demonstration of efficacy in patients with metastatic renal cell carcinoma (MRCC) was based on 2 single-arm open-label phase II studies. Instead, the demonstration of efficacy for the treatment of patients with gastrointestinal stromal tumours (GIST) was mainly based on a double-blind placebo-controlled phase III study. The CHMP considered that the data supported a clinical benefit for Sutent, a favourable safety profile and a positive benefit/risk ratio. The CMA was granted in July 2006 with the specific post-marketing obligations to submit the results of a phase III randomised study, already ongoing at the time of the initial assessment, aimed at demonstrating the efficacy and safety for the MRCC treatment (Motzer, 2009). After just 6 months, in January 2007, EMA recommended a "normal" MA with an extension of the therapeutic indications according to the results of the last study. Alecensa is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) both previously treated with crizotinib and not. It received a CMA in 2017 based on data from two phase I/II studies (EMA, 2016a). As a post-marketing obligation, a clinical study report of phase III, two-arms and randomised study was requested (Peters, 2017). This study was ongoing at the time of granting of the CMA. After 10 months the company was able to demonstrate the superior efficacy of medicinal product. Consequently, the EMA obligations were fulfilled and a "normal" MA was granted. Darzalex® (daratumumab), was initially approved based on data provided by two single arm, phase I/II, open-label pivotal studies (EMA, 2016b) in which adults with multiple myeloma and light chain (AL) amyloidosis were treated. The MAH was asked to submit the results of two phase III

randomized open-label studies comparing the treatment with daratumumab to other therapeutic options (Dimopulos, 2016; Palumbo, 2016). As previously, after 11 months from the CMA a "normal" MA was granted by the EMA.

Caprelsa® (vandetanib) is the medicine that took the longest time to switch, requiring more than 10 (EMA, 2011a). In 2012, it was granted a CMA following a randomized, double-blind, placebo-controlled study (Study 58) conducted to demonstrate safety and efficacy of vandetanib (active substance of Caprelsa) 300 mg versus placebo in patients with unresectable locally advanced or metastatic medullary thyroid cancer (MTC). The result of the primary analysis of progression-free survival (PFS) showed a statistically significant improvement in PFS for patients randomized to vandetanib compared to placebo. In the sporadic form of MTC, "Rearranged during Transfection receptor (protooncogene)" (RET) was found to be mutated (it usually regards the common M918T mutation). The activity of vandetanib in (RET) mutation negative patients was indirectly supported by the activity of the drug observed in the subgroup of patients with RET unknown status. However, it was not certain that those patients tested RET negative for M918T mutation were not positive for mutation on other exons. It was equally not certain that those patients tested RET negative from old tumour sample were still RET negative at the time of initiation of treatment. Therefore, the CHMP considered that there was the need to confirm the benefit risk balance of Caprelsa in patients with (RET) negative mutation. So, the specific obligation for an open label trial comparing (RET) negative and RET positive patients with sporadic MTC treated with vandetanib was imposed to address the missing efficacy data. The study included approximately 60% of patients who received vandetanib within the EU and patients were followed for 2 years. The total duration of the study was expected to be 38 months. Through this study, objective response rate (ORR), progression status and disease control rate (DCR) in the overall population had to be analysed (EMA, 2011a). The specific obligation was fulfilled in 2022 after frequent postponements, meanwhile, in 2020 a paediatric indication was added.

Regarding the EXC, it is noteworthy that, although the conversion of the MA in post-marketing phases should not be expected, 12 authorisations granted between 2002 and 2007 switched into "normal" ones. Such apparent anomaly is justified considering that provisions for CMA have been applied long after the application of EXC's regulatory provisions: in the timeframe between 1995 and 2006 only procedures for "normal" MAs and EXCs were available. Switching occurred after fulfilment of MAHs' specific obligations, including submission of missing data. In particular, 7 out of 12 EXCs switched after 5 years, coinciding with the renewal of the authorisations.

An example is that of Zevalin® (ibritumomab tiuxetan) (EMA, 2005b), authorised in 2004. The safety and efficacy of the Zevalin therapeutic regimen were evaluated in two multi-centre trials enrolling a total of 197 subjects. However, as a specific obligation, a prospective, multicentre, randomised phase III clinical trial (study 304820) was requested to investigate the efficacy and safety of subsequent treatment with 90Y-ibritumomab tiuxetan (active substance of Zevalin) versus no further treatment in patients with stage III or IV follicular non-Hodgkin's lymphoma having achieved partial or complete remission after first line chemotherapy. The primary objective of study 304820 was a difference in progression-free survival (PFS). The clinical trial involved 414 patients, where 208 were randomized to Zevalin and 206 were randomized to no further treatment. Zevalin showed to be effective in significantly prolonging remission-free survival in patients with follicular lymphomas who achieved a response after first-line chemotherapy. Since the specific obligation was fulfilled, in 2009 the EXC switched into a "normal" MA. 5/12 EXCs have been converted at the second renewal of the MAs, thus after 10 years. For example, Aptivus® (tipranavir) (EMA, 2005a) was authorised in 2005 after the submission of data of two open-label, pivotal active-controlled Phase III studies in triple antiretroviral (ARV) class experienced patients [RESIST –1 (1182.12) and RESIST-2 (1182.48)]. The applicant was requested to provide 48-week Clinical Trial Reports for RESIST-1 (1182.12) and RESIST-2 (1182.48) Phase III pivotal trials and 48-week meta-analysis for both studies (Hicks, 2006). In 2007 the specific obligations were changed into "updated data presentation and results for RESIST-1 (1182.12) and RESIST-2 (1182.48) Phase III pivotal trials". In 2008 the MAH submitted these data and no more obligations emerged in the SPC. In 2015 the EXC was converted into a "normal" MA.

4.7 Extensions of therapeutic indications of converted medicinal products

During the time between the granting of CMAs or EXCs and their switch, the applicants requested different types of variations to the terms of the MA. Our analysis focused only on extensions of therapeutic indications, so administrative and quality variations as well as minor changes in SPC, labelling and package leaflet not related to the therapeutic indications have been excluded. Only the switched authorisations (33 CMAs and 12 EXCs) were considered. Sometimes, a variation may correspond to the fulfilment of a specific post-marketing obligation and may fall under distinct categories. Moreover, there may be more than one extension of therapeutic indications for a medicine. In **Figures 4 and 5,** variations occurred before the conversion have been collected and divided into 5 categories: 1) new therapeutic indication different from the authorised one, 2) changes in treatment (line-treatment and combination with other medicines), 3) extension of population by age, 4) extension of population by specific mutation required to have access to the treatment and 5) new pharmaceutical forms.

Many of the considered variations (68% for CMAs and 57% for EXCs) dealt with changes in treatment lines, associations with other medicinal products and patients' stage disease. Some extensions (19% for CMAs and 15% for EXCs) were about the addition of new therapeutic indications, different from those previously authorised [CMAs: Bavencio® (avelumab), Votrient® (pazopanib), Votubia® (everolimus), Libtayo® (cemiplimab) and Crysvita® (burosumab); EXC: Yondelis® (trabectedin)]. For Intelence® (etravirine), Caprelsa®, Crysvita® (CMAs) and Aptivus® (EXC) it was also requested to extend the therapeutic indication also to the paediatric population. In addition, for Aptivus a new pharmaceutical form was introduced. The use of Xalkori® (crizotinib) (CMA) was extended to patients with a specific genetic mutation. With regards to extensions occurred after the conversion (**Figures 4 and 5**), it emerges that, for both CMAs (37%) and EXCs (29%), the majority is related to an extension for paediatric population (extension of population by age); for products with CMA many variations consist in changes in treatments (30%), instead for those with EXCs, both extensions of population by specific mutation and new pharmaceutical dosage forms have been introduced.

5 Discussion

Both CMA and EXC regulatory pathways have been devised to facilitate the obtainment of the MA for medicines used to address unmet medical needs, albeit an incomplete clinical profile at the time of approval. Mainly, CMAs are issued for medicines indicated for the treatment and/or prevention of different types of tumours and their active substances are mostly protein kinase inhibitors and monoclonal antibodies. Instead, EXCs are primarily granted for patients with pathologies affecting alimentary tract and metabolism, then for tumours treatment, and most of them are indicated for paediatric population.

5.1 Are CMA and EXC successful regulatory tools for ensuring patients' access to effective and safe treatments?

CHMP's assessment of a CMA application is based on specific requirements for granting an authorisation. Annex II to the "EMA report on 10 years of experience with conditional marketing authorisations" (EMA, 2017) shows the details about CHMP's negative opinion on the fulfilment of these requirements for some medicines between 2006 and 2016. The analysis of the benefit-risk balance is divided in 6 points: a) failed efficacy study, b) inconclusive results / uncertainties about efficacy / clinical relevance, c) overall insufficiency of data, d) particular safety risk identified requiring more data, e) methodological, GCP and/or statistical issues make data unreliable and f) quality and/or manufacturing aspects. Excluded three withdrawn medicines after positive opinion, the 19 medicines considered have a negative benefit/risk ratio, mostly because of points b), c) and e). In four cases it is established that benefits of early access do not outweigh the risks. Two medicines

do not fulfil an unmet medical need and, for another one, it is considered unlikely that comprehensive data can be provided. Meanwhile 19 medicinal products were rejected, 33 CMAs (included the three applications withdrawn even after a positive opinion by CHMP) were issued. As regards the remaining years, from 2016 to 2022, the CHMP expressed its opinion on 46 applications for CMA and only 5 were not recommended for authorisation because the benefits were found not to outweigh the risks. Some of the concerns aroused by the CHMP were related to the small number of patients recruited in the main studies, the unsatisfactory methods for comparing results of the main studies with historical data for showing medicine efficacy and the conduction of clinical trials.

Certainly, the absence of some clinical data at the time of approval may raise concerns about the real efficacy and safety of a medicinal product. However, it is noteworthy that quality and, partially, efficacy and safety requirements of medicinal products are met. Indeed, for example, from the EPARs of the four medicinal products analysed in the paragraph "Converted authorisations" (EMA 2006; EMA, 2011a; EMA 2016a; EMA, 2016b), no concerns have arisen for those data since they were sufficient for the proposed therapeutic indications. Instead, more data were requested for clinical efficacy and safety, since 52% of medicines were authorised without phase III clinical trials and 20% with ongoing phase III studies at the time of approval.

From our study, it emerges that the CMA regulatory pathways maintains the ability of assessing the risk-benefit balance: indeed, only 3 of 71 authorisations have been withdrawn between 2006 and 2022, 2 of which for commercial reasons, thus, not related to the efficacy or the safety of the medicines, and 1 for lack of efficacy, while no CMA product has been withdrawn for toxicity/safety concerns. Moreover, CMA products have to fulfil European pharmacovigilance requirements for medicines under "additional monitoring." As other products under additional monitoring, they have a black inverted triangle displayed in their package leaflet and in the summary of product characteristics and are subjected to a stricter monitoring of adverse drug reactions (EMA, 2023d). Based on the above considerations, it is worthy considering that undetected risks for public heath are negligible. After fulfilling the post-marketing obligations, 33 of 71 products have switched to standard authorisations. This means that, despite of the lower amount of clinical data provided at the moment of CMA application, the initial benefit-risk balance has been confirmed in the post-marketing phase. Although basing the benefit/risk assessment on interim clinical results may expose to the risk of withdrawing authorized medicines if superior efficacy is not demonstrated when complete clinical data become available (Faust, 2012), in almost all cases, the use of the CMA undisputedly allowed to promote an earlier patients' access to essential treatments.

A similar trend was observable for EXCs. Between 2002 and 2022, 65 applications for EXCs have been submitted and three of them have been refused. One of these medicines is Heparesc® (human heterologous liver cells), meant to be used in the treatment of severe urea cycle disorders. According to CHMP's opinion, it has been refused because the efficacy of Heparesc has not been sufficiently demonstrated and its benefit/risk balance was unfavourable (European Commission, 2015). In 2004 an application was submitted for Yondelis®, an antineoplastic agent, but its efficacy was not properly or sufficiently demonstrated (European Commission, 2004). After 2 years from the refusal, the MAH made another request submitting more convincing data, and the authorisation was released in 2007. Similarly, the application for Raxone® (idebenone) was refused at first for lack of efficacy (European Commission, 2013), but the following year, it obtained a positive opinion by CHMP and an EXC was granted. Therefore, only one application for EXC have been definitively refused out of 65. About the authorisations released, only one has been withdrawn for lack of efficacy (Xigris®) and no one for safety/toxicity concerns. Even if the MAH is not expected to be able to provide full comprehensive data, specific obligations imposed by EMA should be fulfilled. When the MAH fails in this, the medicinal product should be withdrawn, as happened with Onsenal®. Moreover, it is noteworthy that the number EXCs per year significantly decreases from the period 2002-2007 (3.3 ± 0.6) to 2008-2022 (2.1 ± 0.4; Student's T Test; $p = 0.04$). Such evidence may be justified considering that CMA regulatory framework had not been adopted yet between 2002-2007. Indeed, as mentioned above, the current regulatory framework allows to discriminate products that required conditional approval from those that should be placed on the market in exceptional circumstances.

5.2 Critical issues still on the ground

Although the CMA has been introduced by the EU Legislator as a temporary status to facilitate patients' access to innovative and essential pharmacological treatments, for some medicines [e.g., Sirturo® (bedaquiline fumarate), Deltyba® (delamanid) and Translarna® (ataluren)] the CMA have been renewed more than 7 times. Although detailed motivation is not publicly available, such delays are generally due to challenges in completing clinical trials and/or difficulty in patients' recruitment. In some cases, the trials duration is longer than the 1-year CMA validity. Moreover, deadlines for post-marketing obligations are frequently postponed without publicly apparent causes. The average time for switching to a "normal" MA is 4.0 ± 2.7 years. However, the switching period differ significantly among CMAs based on the availability of phase III clinical trials at the moment of CMA granting. Indeed, CMAs with completed phase III clinical trials required about 5.3 ± 3.1 years to grant a "normal" MAs. On the contrary, for CMAs with no phase III clinical trials submitted, the switching period took 3.3 ± 2.2 years ($p = 0.03$; Student's T Test). In the end, it took 2.4 ± 1.6 years for CMAs

with ongoing phase III clinical trials ($p = 0.03$; Student's T Test). Not even the submission of complete phase III clinical trials can guarantee an obtainment of standard MA in a short time.

A revision of the CMA regulatory pathway seems useful to optimize the conversion rate of CMAs to ensure fulfilment of regulatory obligations for MAHs and avoid unnecessary regulatory costs. According to the provided data, most medicinal products switch to non-conditional MA in about 2-4 years. These results cast a doubt on the effectiveness of the current CMA pathway, especially in terms of the timing schedule. Indeed, the obtained results seem to suggest that one-year validity of CMA proves usually to be insufficient for fulfilling the regulatory obligations and for providing missing data of clinical trials. On the other side, the administrative processes connected to CMA renewal may be justifiable for the first renewals, when the regulatory need to monitor the medicinal product is more urgent, but not in a more mature phase of the CMA (i.e., after 4 years from first authorisation). Indeed, in the latter scenario, the management of one-year validity of CMA may result in unjustified costs and overloads for both industrial and regulatory stakeholders. Consequently, a switch from a fixed one-year validity of the CMA to a flexible time-based scheme - e.g., a one-year validity for the first two years, followed by a two-year validity from the third year - may help striking a balance between the fulfilment of regulatory obligations and products' economic sustainability. Of course, this approach cannot be applied to medicinal products for which quality and pre-clinical data are not complete at the time of first application, for example products authorised in emergency situations (e.g., covid-19 outbreak) for which an annual renewal is more suitable. The stretching of CMA validity should be linked to tight monitoring programs in the post-marketing phases to assess trials' progression. Indeed, following the example adopted for accelerating the pre-marketing assessment process, a rolling review of the progression of clinical trials may result in a better and quicker assessment of the benefit/risk balance of the medicinal product, avoiding delays due to process inefficiencies and improving the transparency on the causes beyond repeated renewals of CMAs.

The results obtained highlight that, for some medicines, switching can take an extremely long time. After a considerable period (more than 8 years), the renewal of a CMA seems illogic, and other possible strategies should be singled out to ensure patients' access to therapy. Firstly, considering the difficulties in performing a proper clinical trial, available real-world data on efficacy and safety could be used in support of the benefit/risk assessment for CMA products. Indeed, in the last decades, the use of real-world data to support decision-makers in assessing proper reimbursement policies and to speed-up regulatory approval for placing products on the market (Crisafulli, 2019; Justo, 2019; Tan, 2023) has been increasing for many purposes, including safety monitoring. Secondly, it may be suggested converting the CMA into an EXC, the rationale being the evident impossibility from the

part of CMA holders to provide the missing data. Indeed, for granting an EXC, the MAH should demonstrate to the CHMP that it is impossible to provide comprehensive clinical data for scientific or ethical reasons. In the case of long-standing CMAs such demonstration may be documented by the review of unfulfilled obligations by the MAHs.

6 Conclusions

CMA and EXC are regulatory pathways provided by EU legislator to address unmet medical needs by making available authorised medicines in a brief time. In the case of the CMA, medicines are placed on market without comprehensive clinical data. In the case of EXC, the MAH cannot submit them for specific reasons foreseen by law. Our study shows that the CMA and EXC pathways to not pose reasonable concerns for patients' health regarding efficacy and safety with respect to a standard assessment process. Indeed, only one out of 71 CMAs granted since 2006 and only one out of 51 EXCs granted since 2002 have been withdrawn for lack of efficacy and none for safety/toxicity concerns; such findings do not depart from trends of medicines authorized by the EMA following the standard centralized procedure. Of course, having a complete profile of a medicine is essential, and any CMA is meant to be converted into a "normal" MA as soon as the missing data are available. However, some CMAs have been renewed several times before they have been replaced with MAs not subject to specific obligations. This is mainly due to delays in completing clinical trials and additional studies imposed as specific post-marketing obligations. To solve this problem, some solutions can be put forward. On the one side, for the pre-marketing phase, this may be reached by expanding the use of rolling review by the EMA to start the benefit-risk balance assessment of the product as soon as preclinical/clinical data are available, as successfully demonstrated by the regulatory process that result in the authorization of COVID-19 vaccines. On the other side, for the post-marketing phase, a closer monitoring of the EMA upon the work of companies in fulfilling their duties might be necessary.

Moreover, it may be a sensible move to extend the validity of CMA to 2 years, instead of 1, to reflect the fact that, on average, the switches to a "normal" MA have occurred after 4 years. It could also be proposed that real-world data demonstrating efficacy are used for converting a long-standing CMA to a "normal" MA or, as an alternative, that a long-standing CMA is converted to an EXC, if the MAH can demonstrate and properly justify the impossibility of submitting the missing clinical data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Sara Manellari: Data curation, Formal analysis, Investigation, Roles/Writing - original draft

Umberto M. Musazzi: Conceptualization, Methodology, Writing - review & editing

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Paola Minghetti: Conceptualization, Methodology, Supervision, Writing - review & editing

7 Tables

Table 1 – Main features of CMAs and EXCs.

	CMAs	***EXCs***
Legal sources	Regulation (EC) No. 726/2004; Commission Regulation (EC) No. 507/2006	Regulation (EC) No. 726/2004; Directive 2001/83/EC
Access criteria	Seriously debilitating or life-threatening diseases, emergency situations, rare diseases	Applicant unable to provide comprehensive efficacy and safety data because: - the indications are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or - in the present state of scientific knowledge, comprehensive information cannot be provided, or - it would be contrary to generally accepted principles of medical ethics to collect such information.
Post-marketing commitments	MAH required to complete ongoing studies, or to conduct new studies	MAH not required to complete ongoing studies, or to conduct new studies
MA validity	one year, on a renewable basis	Reviewed annually to assess the risk-benefit balance, in an annual re-assessment procedure
Switching to standard MA	Once the pending studies are provided	Not applicable

MA = Marketing Authorisation; MAH = Marketing Authorisation Holder.

Table 2 – Availability of results of phase III trials at submission of first application of medicinal products then authorised following CMA regulatory pathways.

Phase III trials	***CMA applications***		***Non-conditional MA applications, converted in CMAs on CHMP advice***	
	Current (n=35)	*Converted (n=33)*	*Current (n=22)*	*Converted (n=11)*
No	22 (62.9%)	14 (42.4%)	9 (40.9%)	4 (36.4%)

Yes, ongoing	7 (20.0%)	5 (15.2%)	2 (9.1%)	1 (9.1%)
Yes, complete	6 (17.1%)	14 (42.4%)	11 (50.0%)	6 (54.5%)

8 Figures

Figure 1 – Flowchart from applications to current CMAs (a) and EXCs (b).

Figure 2 – Number of CMAs and EXCs released by EMA, medicinal products authorised as CMAs/EXCs that were converted to normal MAs, and medicines' withdrawal between 2002 and 2022.

Figure 3 – Medicinal products, for which CMAs (a) and EXCs (b) have been granted, divided by ATC codes.

Figure 4 – CMAs' extensions of therapeutic indications before (a) and after (b) MA conversion.

Figure 5 – EXCs' extensions of therapeutic indications before (a) and after (b) MA conversion.

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