Early access in the EU: a heterogeneous landscape with room for harmonisation

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KEYWORDS

Early access programme (EAP); Harmonisation; Compassionate use programme (CUP); Named patient programme (NPP); National competent authority (NCA); European Medicines Agency (EMA); EU member state (MS).

ABSTRACT

The existence of a regulatory framework that enables pre-licensing access to medicinal products on the basis of a presumed positive benefit–risk ratio undoubtedly offers timely access to potentially life-saving and innovative products to patients living with diseases representing an unmet medical need. We performed a study to assess whether the current framework of regulations results in a well-harmonised approach for early access programmes (EAPs) across the 27 EU member states plus the UK.

The results of our study revealed significant heterogeneity exists across countries, not only in the availability of national EAPs but also on how well-defined the programmes are in relation to key administrative and operational requirements. Our findings point to important considerations, both positive and negative, that stakeholders should provide careful thought to before implementing an EAP throughout European countries.

With the potential to improve the speed of access to important and innovative medicines in areas of critical unmet medical need, we believe that greater regulatory harmonisation is required to widen the early access of potentially life-saving therapies throughout the countries analysed.

Introduction

Therapeutic innovation in recent years, especially for the treatment of cancer or rare and serious diseases, offers the promise of improving patient survival and quality of life. However, the drug development process is notoriously lengthy and paved with failures. For those patients who have exhausted commercially available therapeutic options, access to drugs with a presumed favourable benefit–risk ratio before the marketing authorisation and pricing/reimbursement process is complete could be a lifeline. In exceptional times, such as the current SARS-CoV-2 (COVID-19) pandemic, when no approved therapy is available, the use of promising development products offers the potential to address serious unmet medical needs.

In Europe, access to unauthorised medicines is possible outside of clinical trials via either: (1) compassionate use programmes (CUPs) for a group of patients, or (2) named patient programmes (NPPs) for individuals. The notion of humanitarian or compassionate use emerged in the late 1980s during the fight against the HIV epidemic.[1] At the time, HIV patients advocated for an earlier access to treatment, given the considerable time needed for their development, and subsequent authorisation. Discussions between patient organisations and health authorities played a major role in enabling patients worldwide to gain access to experimental antivirals. Since then, the CUP framework has evolved tremendously around the world and has been developed and implemented in many countries.

Although an EU framework exists, these programmes are coordinated and implemented by EU member states (MSs), which set their own local rules and procedures. Thus, access to drugs before their authorisation remains a national decision, based on national regulations, with national competent authorities (NCAs) as the gatekeepers.

We report here the result of a study aimed at comparing CUPs and NPPs in the EU MSs, and the UK.

Definitions of CUP and NPP

CUP Established by Article 83 of Regulation (EC) No 726/2004,[2] the compassionate use of a medicinal product makes an unauthorised product available to a group of patients with seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by any authorised medicinal product. The criteria for eligibility to a CUP are shown in Table 1.

Article 83 is not applicable to: (1) medicinal products which are not eligible for the centralised procedure (CP), (2) compassionate use on a named-patient basis, or (3) a medicinal product which has already been authorised via the CP, even if the proposed conditions of use and target population are different from those of the marketing authorisation (MA).

It should be noted that although the Regulation of the European Parliament establishes a general legal framework, CUPs fall under national jurisdiction and, in most MSs, under the remit of NCAs. Therefore, the national regulatory framework is complementary to Article 83. Similarly, the European Medicines Agency (EMA) can provide recommendations in order to complement national legislation but these cannot supersede national legislation.[3] An option exists for EU MSs to request/receive a scientific opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) on how to administer, distribute and use certain medicines for compassionate use. Guidance is also available from the EMA on the criteria and the procedure for using the CUP.[4]

Although such CHMP opinions are not binding, MSs shall take into account available recommendations when administering their CUPs. It is noteworthy that only a limited number of opinions have been published by the EMA since 2005 (see Table 2),[5] and thus requested by MSs. These have been limited to antivirals for treating influenza, following the H1N1 influenza virus pandemic of 2009, and for hepatitis C at a time of major changes in the standard of care. More recently, an opinion was granted

TABLE 1

Comparison and key characteristics of CUP and NPP

Programme	CUP	NPP
Regulatory framework	Article 83 of Regulation (EC) No 726/2004	Article 5 of Directive 2001/83/EC
Definition	The compassionate use of a medicinal product consists of making a medicinal drug not yet authorised available to a group of patients with long lasting or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by any authorised medicinal product.	An MS may fulfil special needs formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his/her direct personal responsibility.
Who benefits from the programme	A group of patients.	Named patient(s) for whom the request has been made.
Procedure	• Country-specific. • Falls under the remit of NCAs and, in some cases, ECs. As a result, procedures vary for each country. • The NCA in the MS decides if such a programme fulfils an unmet medical need according to its clinical practices and available alternatives.	Country-specific.
Eligibility criteria	Eligible medicinal products must be undergoing clinical trials or have entered the MAA process. The group of patients has a long lasting or seriously debilitating disease or the disease is considered to be life-threatening, and cannot be treated satisfactorily by any authorised medicinal product. Patients are not eligible to participate in ongoing clinical trials. Does not cover off-label use of an authorised medicinal product.	• Eligible medicinal products may include authorised or unauthorised medicines and decisions are made on a case-by-case basis. • Patients should always be considered for inclusion in trials before being offered an NPP.
EMA role	• NCAs should inform the EMA if they are making a product available to a group of patients under a CUP and have the option to request a CHMP's scientific opinion. • The EMA's CHMP can provide recommendations in order to complement national legislation but do not replace it.	The EMA is not involved in NPPs and does not need to be informed by NCAs.

CHMP: Committee for Medicinal Products for Human Use; **CUP:** Compassionate use programme; **EMA:** European Medicines Agency; **EC:** Ethics committee; **MAA:** Marketing authorisation application; **MS:** Member state; **NCA:** National competent authority; **NPP:** Named patient programme.

for remdesivir, a therapeutic option for COVID-19.[6] This opinion was later updated based on a rolling review by the EMA of the remdesivir data for COVID-19.[7] Depending on the rapid evolution of the COVID-19 pandemic, one may speculate that other products may be granted an opinion.

NPP NPPs are designed for the supply of unauthorised medicines in response to unsolicited requests for drugs for individual patients, pursuant to Article 5 of Directive 2001/83/EC.[8] NPPs may cover access to a non-authorised medicine at any time of its development, provided it is not made available under a CUP. The criteria for eligibility for NPPs are shown in Table 1.

NPPs, like CUPs, are governed by individual MSs legislation and, as a result, are not harmonised across countries in Europe. Decisions are made on a case-by-case basis and examples of uses under NPP include drugs that are: (1) approved but not yet commercially available to be prescribed in the patient's country, (2) approved and available in one country but not approved and available in the patient's country, (3) discontinued in the patient's country but not in another, (4) in shortage in the patient's country but not in another, (5) administered in a clinical trial which has now ceased and under which the patient showed improvements, (6) undergoing clinical trials for which the patient is not eligible, but where the patient would benefit from the treatment. Table 1 provides an overview of the key features and differences between the CUP and NPP.

Design and methodology of the study

Information on the CUP and NPP for the 27 EU MS+UK was collected in Q1 2019 through NCA websites and/or ministries of health websites, literature review, and by online search using country-specific search terms from the healthcare domain. NCAs were also directly contacted in instances when information was not readily available online.

A table summarising our findings for the CUP and NPP in the 27 EU MS as well as in the UK will be published in a subsequent issue of this journal.

Results

General conditions. According to our findings, 21 countries (75%) currently have a national regulatory framework in place for CUPs involving NCAs, and in some cases ethics committees (ECs), in the approval process. For most countries, the conditions for CUPs correspond to the transposition of the EU regulation into national laws; however, some discrepancies and differences exist. In Estonia, the law specifies that the medicinal product concerned should have successfully completed at least Phase II trials, and in Italy different provisions apply to medicines that have completed Phase III, Phase II or Phase I studies. In Romania, the specific therapeutic areas that may be subject to a CUP application are specified.

NPPs exist in 23 countries (~82%), however, the framework is more

TABLE 2

Summary of EMA opinions under Article 83 (as of 8 July 2020)[5]

Molecule	Target population	Date of opinion	Status
Oseltamivir phosphate	Critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic A(H1N1)v infection or infection due to seasonal influenza A or B virus (and answering specific criteria).	20 January 2010	Closed
Zanamivir	Critically ill adults and children having a life-threatening condition due to suspected or confirmed pandemic A(H1N1)v infection or infection due to seasonal influenza A or B virus (and answering specific criteria).	18 February 2010	Closed
Sofosbuvir	Adults infected with chronic hepatitis C who are also: ● Actively on the waiting list for liver transplantation (documented) and require treatment to prevent graft reinfection with hepatitis C virus, or ● Who have undergone liver transplantation and have aggressive, recurrent hepatitis C infection resulting in progressive and worsening liver disease, and are at a high risk of death or decompensation within 12 months if left untreated.	24 October 2013	Ongoing*
Daclatasvir	In combination with sofosbuvir +/– ribavirin, for genotype 1 patients above 18 years of age who are at a high risk of decompensation or death within 12 months if left untreated.	21 November 2013	Ongoing*
Ledipasvir/ Sofosbuvir	As a fixed dose combination, +/– ribavirin in adults infected with chronic hepatitis C genotype 1 virus, with advanced disease who are at a high risk of decompensation or death within 12 months if left untreated.	20 February 2014	Ongoing*
Remdesivir	● Adults with coronavirus disease 2019 (COVID-19) who require invasive mechanical ventilation. ● Expanded to include hospitalised patients who need supplemental oxygen, non-invasive high-flow oxygen devices or extracorporeal membrane oxygenation (ECMO).	2 April 2020 (initial) 11 May 2020 (updated)	Ongoing*

*CUP opinion status shown as "ongoing" on the EMA website although an EC decision was received for these products (note, daclatasvir is no longer authorised in the EU).

diverse – while some NCAs have a regulatory framework *per se*, involving agencies and/or ECs, others only provide a description of the conditions under which a non-authorised product can be used (eg, urgent, life-threatening conditions, with no alternative therapeutic option); in those cases, prescription of the unauthorised medicinal products falls wholly under the competency of the physician.

Differences exist in the naming of the programmes: some countries refer to CUP/NPP as an "early access programme (EAP)" (Greece, Portugal), while others have introduced specific terminology such as France (temporary authorisation for use [ATU]) and the UK (early access to medicines scheme [EAMS] for CUP). The term EAP may cover CUP and NPP but also refers to access in the period of time between the granting of an MA and completion of the pricing/reimbursement process. In Europe, the term "expanded access" usually refers to access for patients who have received a drug during a clinical trial and who wish to continue treatment after the trial ends.

In some MSs, the same legal framework covers both CUP and NPP under the term "compassionate use" (Denmark, Finland, Spain). Some countries have NPP and no CUP (eg, Hungary, Ireland) and vice versa (Croatia, Romania).

Administrative aspects. In most MSs, an application for CUP can be made by the (future) applicant for the MA. Some MSs extend this to different stakeholders such as the sponsor of the clinical trial, other organisations (eg, the Minister of Health, scientific organisations) or natural or legal persons. For NPPs, our analysis suggests applications may be made, for example, by the treating physician or a group of physicians, patient associations, hospital or pharmacies.

The maximum duration for CUPs is specified for most countries and either expire on commercial availability of the authorised medicinal product or have a specified duration – usually 6–12 months – which can be extended or renewed.

The application process for CUP and NPP varies in details and complexity from country to country. For some MSs, a full step-by-step process with details of the requested documentation is provided (Austria, Belgium, France, Germany, UK – for CUPs), while for others there is little or no information readily available. For CUPs, the review and approval timelines were not always available, and where information was provided, this varied between five days (Portugal) and three months (Austria).

As CUPs are nationally implemented, it is at the discretion of the NCA whether to apply a fee for the application. For France, Germany or Sweden, the application process is free, but a fee is applicable in the Czech Republic and in Austria. At the time of our research, this information was not always available.

Sponsor, MS and physician responsibilities. For countries with a CUP in place, one of the key responsibilities of the sponsor (CUP holder), MS or physician concerns safety reporting and pharmacovigilance, specifically the reporting of suspected adverse reactions (SARs) and, in some cases, the submission of development safety update reports/periodic safety update reports (DSURs/PSURs) as detailed in Good Pharmacovigilance Practice VI.C.1.2. Although not part of this analysis, our research suggests implementation may differ across MSs, and that different reporting obligations apply for different MSs. For some countries such as Croatia, Malta and Luxembourg, reporting responsibilities could not be readily identified in national laws. In others, where sponsor responsibilities include SAR reporting to NCAs, timelines were usually specified (eg, Czech Republic, Denmark, Germany, Romania). Reporting obligations also apply to NPPs, however these are generally less well-defined than for CUPs. Therefore participating companies should check responsibilities for each participating country.

Specific provisions exist in some MSs concerning the requirement to collect additional data, the nature and level of data to be collected, and the

use of the data. In Italy, the law specifies that, although the data collected as part of the CUP does not replace the data requirement for a marketing authorisation application (MAA), it can be supportive. In contrast, in Greece, data collected in CUPs cannot be used in the MAA dossier. In France, when a medicinal product is used in a CUP during MAA stage, the applicant must ensure that all of the information made available in the context of the CUP and impacting on the benefit–risk ratio has also been reported to the competent authorities currently assessing the MA application. These discrepancies raise questions over data on drugs used in national CUPs which are then filed for MAA under the CP.

Can a CUP product be charged and reimbursed? Where information was available (15/21 countries), companies provide a CUP product for free in ~67% (10/15) of countries, while only ~33% (5/15) of countries allow a fee to be levied for these drugs. For NPPs, the available data show that a fee is charged for the medicinal product in ~43% (10/23) of countries.

Discussion

The analysis performed across the 27 EU MS+UK provides valuable information for key stakeholders including regulators and patient advocacy groups. It is also especially relevant for smaller biotechs and small and medium-sized enterprises (SMEs) when considering making their as yet unlicensed medicinal products available to patients, on the basis of positive clinical data supporting a preliminary but positive benefit–risk ratio in a condition where there is a clear unmet medical need. Although our research did not specifically investigate therapeutic areas within CUP/NPP, it is worth noting that drugs being granted CUP encompass a variety of therapeutic areas including, but not limited to, orphan diseases, oncology and infectious diseases.

Our findings reveal substantial variation between countries not only in the availability of early patient access arrangements to unlicensed medicines either through CUP or NPP, but also in the way these programmes are managed at national level. All of this may have a serious impact on the likelihood of a patient with a seriously debilitating or life-threatening condition having access to a drug with significant benefit. These are also important considerations for companies when selecting the most appropriate countries that fit with both their strategic objectives of entering into an EAP and the level of internal resource that would be required to support the scheme in that particular country. Although our data may allow readers to consider which are the most attractive countries for an EAP based on key criteria, relating largely to how well national EAPs are defined, additional considerations need to be taken into account as revealed by a European Federation of Pharmaceutical Industries and Associations (EFPIA) analysis on market access to approved drugs across MSs.[9]

Heterogeneity exists amongst countries. Our study shows there is a lack of harmonisation or common approach when considering CUPs across the MSs. This is evidenced by inconsistency in naming conventions, national legal frameworks not aligned with the Regulation, different methods of administering the system and differences in reporting obligations. It is possible that national authorities and other key stakeholders may take divergent views on CUPs due to specific national requirements, including national differences in availability of treatment options, national medical practice, available resources, funding, and potential different points of view in regard to assessment. The heterogeneity across MSs was highlighted in a recent paper from the Heads of Medicines Agencies (HMA),[10] where action points around the need to harmonise the terminology employed to refer to EAPs, the application process, and the information provided on the HMA website and websites of NCAs were identified. This lack of harmonisation across EU MSs, which requires local interaction with individual NCAs, has created a significant burden, particularly for SMEs, which may not have the required local presence and capacity to manage this level of heterogeneity. Whether this impacts the level of access for European patients remains a question to explore.

As the role of the EMA is non-binding, the possibility for a centralised and more transparent administration of CUPs is perhaps being under-utilised. It is indeed striking that only a few molecules have been granted an opinion from CHMP under Article 83, and that those are exclusively antivirals (see Table 2). This suggests that MSs have sufficient capacity to generate scientific assessments and form their own opinion on the administration of CUPs, despite having the possibility to request a CHMP opinion. On the other hand, there is evidence that EMA guidance was sought in situations such as pandemics and major therapeutic changes in widespread diseases (Table 2).

The information gathered during this study shows that any stakeholder planning a CUP in the EU is faced with a patchwork of national regulations. This lack of harmonisation is likely impacting patients' access to medicines via CUPs, with resulting prolonged suffering of sick individuals, and thus opposing the objective of the Regulation. For example, access opportunities may be dependent on where a patient lives and whether the country has a framework supporting a well-managed CUP in the first place. Companies, particularly SMEs, may choose to avoid applying to national systems that appear administratively burdensome, or have high fees associated to the application, particularly where the timing of entering an EAP coincides with the preparation for filing an MA.

From a financial perspective, differences in application costs and national reimbursement policies for medicines available under EAPs exist between countries. This could be a major factor impacting the EAP strategy, especially for biotechs or SMEs, as many MSs recommend that the product is made available for free. In particular, this could be a barrier for companies developing products that are expensive to manufacture.

It is important to recognise the regional variation that exists throughout MSs in the access to medicines following approval by the EMA, and how this may influence company strategy on selection of countries in which to target EAPs. The health technology assessment (HTA) process is not EU-centralised, with the decision on the reimbursement or pricing being taken nationally. An analysis conducted by EFPIA on market access delays, comprising a sample of 146 products approved by EMA between January 2014 to December 2016, highlights these regional variations.[9] Therefore when planning their EAP strategy, companies need to be aware that EAPs initiated prior to MA will continue for variable periods following approval. Some countries, including France, have introduced national laws to avoid disruption to treatment during this period.

The pros and cons of EAPs. From the patient's perspective, having the possibility to access a promising drug before it is registered or commercially available carries the obvious advantage of potentially reducing suffering or even extending survival. However, the hope of a possible benefit from the treatment will be balanced against the potential risks that should be explained in detail by the patient's physician. Although not as strictly defined as in a clinical trial, the enrolment into an EAP may still be defined by inclusion criteria and patients may need careful explanation of the reasons for being denied access to a treatment that they believe could offer hope. The economics should not limit access to a medicine once it is within the framework of an EAP. In cases where the treatment is subject to a charge by the pharmaceutical company, this would normally be covered by healthcare insurance or the national healthcare system.

From the physician's perspective, offering an innovative drug to patients enriches their role as a well-informed practitioner at the forefront of therapeutic innovation. There may also be the possibility of publishing the results of the programme. However, when the programme is defined by a specific protocol, the patient or eligible population is well-defined and the freedom to prescribe is not as broad as when a drug is commercially

available. Furthermore, physicians often consider that CUPs and NPPs come with a significant administrative burden and this can result in non-compliance with these requirements.

From the pharmaceutical industry's perspective, making the drug available in one or several MSs before MA gives a signal that the NCA has assessed the drug as having a presumed, preliminary positive benefit–risk ratio. Although assessment by the NCA does not replace or preclude a positive opinion from the CHMP, this anchors the drug as a candidate for an MAA. In practice, it is not infrequent that companies first assemble their MA dossier and use it for CUP applications. It is also valuable for the company that physicians who did not participate in the clinical trials have access to the drug and build awareness around the credibility and value of the product among key stakeholders. At this stage of the drug's lifecycle, the collection of safety events is critical to the confirmation of its safety profile; therefore the conditions for careful pharmacovigilance are essential and some companies may be reluctant to open CUPs if they believe the conditions for reliable data collection are not met. It is important to note that the Regulation demands that pharmacovigilance is applied to these programmes. Having the possibility to charge for drugs provided as part of a CUP is an attractive feature in some countries; this may be marginal for large pharmaceutical companies and conversely significant for small biotechs and SMEs. Nevertheless, participation in CUP in some countries such as the UK provides an opportunity to engage with relevant HTAs which could accelerate access following approval.

Real-world data. A key benefit of EAPs is the opportunity to generate real-world data (RWD) which, in some instances, could be used to support an MAA and/or technology appraisal.

Companies may use the EAP to gather data on the potential benefit of drugs without the strict boundaries of the inclusion/exclusion criteria of clinical trial. RWD can provide insights on how the product behaves in a patient population which has comorbidities, concomitant medications and demographic variabilities. It can also help to provide safety data, knowledge on the impact of the drug on quality of life, treatment effectiveness and drive label expansion for rare diseases and other patient populations not originally studied. The EMA guidance does not prohibit data collection beyond safety outcomes, however, it does state that these programmes should not be viewed as a substitute for clinical trial data.[4]

A critical issue with the collection of RWD in CUPs is that the regulatory environment for data collection is not consistently defined across MSs. Our research revealed that, although some countries have sophisticated systems in place, this is not always the case and should therefore be carefully considered. In addition, the lack of means given to physicians in some countries to collect data as part of CUPs is a hurdle. Because communication to physicians involved in CUPs is controlled by NCAs, it is also not possible to perform monitoring of the data collection as in clinical trials. Finally, the proprietary nature of the data generated during CUPs is also of importance as the sponsor has to obtain endorsement of the national authority for use of the data.

As a topical example at the time of writing, a CHMP opinion on the compassionate use of remdesivir had been issued at the request of Estonia, Greece, the Netherlands and Romania (see Table 2), and the UK Medicines and Healthcare products Regulatory Agency had issued a scientific opinion under the EAMS for use of remdesivir in COVID-19 (26 May 2020). Although it is anticipated that valuable RWD will be generated as part of these programmes, notably on the safety of the treatment, randomised clinical trial(s) will be necessary to determine the true benefit–risk profile of this treatment.

Conclusion

Offering early access to drugs to severely ill patients who cannot be treated satisfactorily by an authorised medicinal product is undeniably beneficial to patients and caregivers, as well as serving a public health prerogative. This positive environment has its roots in the major health crisis of HIV infection and it speaks to the foresight of NCAs, the EMA and political decision-makers to have made this possible. Nevertheless, since the advent of CUPs in Europe, our research has shown that significant heterogeneity still exists amongst European countries. As a consequence, unfortunately European patients in some countries have less opportunity to receive potentially life-changing or even life-saving new drugs compared with their counterparts in neighbouring countries. Additionally, this heterogeneity makes it more complex for stakeholders to apply for and administer CUPs throughout Europe. It is also noteworthy that the number of opinions granted through the Article 83 procedure by the EMA remains limited. One may question whether this procedure could be more frequently used by MSs to obtain guidance from the EMA and improve consistency of patient access and exposure throughout Europe. It is reassuring to see that this has been done in the case of the COVID-19 pandemic. CUPs are also a relevant source of RWD, mainly from the safety perspective but also from an effectiveness standpoint if rigorous data collection is ensured; these RWD may complement data for regulators, HTAs and payers alike. ■

ACKNOWLEDGEMENTS

Mariana Arroja is acknowledged for her input in the initial planning of this manuscript.

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