LEADING ARTICLE

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EU Compassionate Use Programmes (CUPs)

Regulatory Framework and Points to Consider before CUP Implementation

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Abstract

For some patients, compassionate use programmes (CUPs) are the only way to access promising medicinal products that are not yet authorized and for which clinical trials are either not available or in which these patients cannot participate. For such patients, the CUP benefits can be very important. Although an EU regulatory framework exists, there is no single, centralized EU-wide procedure for CUPs. Each Member State has its own procedures and CUP approvals are governed by national regulatory authorities. This article provides an overview of the regulatory frameworks in the EU for CUPs and includes a discussion of the different types of programme available, eligibility criteria, key points for industry to consider and related pharmacovigilance obligations.

There are two major types of CUPs, commonly referred to as named patient compassionate use programmes (NP-CUPs) and cohort compassionate use programmes (Coh-CUPs). NP-CUPs are typically initiated by physicians for an individual patient in great need of a medicinal product, which will be administered under the physician's responsibility. Companies usually have little influence on this type of CUP. However, companies can try to anticipate these demands and define in advance a set of criteria allowing safe access and administration to these patients. Coh-CUPs are usually defined programmes initiated by the manufacturer to allow access for a group of patients to an unauthorized medicinal product. Both NP-CUPs and Coh-CUPs are allowed under strict conditions only. A key point for a successful CUP is to manage stakeholders' expectations and to have a good level of communication with patients and physicians, although it is strictly forbidden to promote the use of unauthorized medicinal products. In addition, a CUP needs to be well controlled, and risks carefully anticipated particularly with regards to safety aspects. In terms of financing, there is no general rule with regards to the possibility of charging for these medicinal products under CUP. It depends on the country and on the type of programme. For some countries, it is often on a case-by-case basis. Thus, this should also be factored in to the budget. Importantly, in some countries, such as France, the price of a medicinal product established in a CUP will influence future price negotiations after the medicinal product is granted marketing authorization, as well as the timing of these negotiations. In such cases, it can be difficult to obtain a higher price than was applied in the CUP and it is wise to conduct pharmacoeconomic studies prior to proposing the price for the product during the CUP. Finally, if a CUP is anticipated, companies should plan their internal and external resources. Important resources include a project manager supported by a medical person, as well a person in charge of the pharmacovigilance aspect and an EU importer/distributor.

There are many factors to take into account when a medicinal product is expected to be solicited in a CUP, whether NP-CUP or a Coh-CUP. Careful planning for a CUP is critical and should take into account the perspective of the treating physician and the patient, as well as the national regulatory frameworks.

Supply of medicinal products under compassionate use provides eligible patients with access to unlicensed therapies. For such patients, the benefits can be very significant. Typically, compassionate use programmes (CUPs) are initiated late in the development of medicinal products to 'bridge' the time between the end of phase III development, regulatory approval and product launch (which may take 1–2 years).

The objective of this article is to provide an overview of CUP regulatory frameworks in the EU, including discussion of the different types of programme available, eligibility criteria and

key points for industry to review, including related pharmacovigilance aspects, when considering the implementation of a CUP.

1. Overview of Compassionate Use Programmes (CUPs) in the EU

1.1 EU Regulatory Framework

Medicinal products must obtain regulatory approval before they can be marketed in the EU.

At the EU level, exemptions were created in 2001 with Directive 2001/83/EC[1] and in 2004 with Regulation 726/2004/EC[2] to provide a regulatory framework for access to unauthorized medicinal products intended to treat, prevent or diagnose a disease in humans.

Compassionate use regulations have evolved over time, starting, in 2001, with relatively vague language about the possibility of making unauthorized medicinal products available for an individual patient (Article 5 Directive 2001/83/EC).[1] In addition, the Directive allowed Member States to temporarily authorize the distribution of an unauthorized medicinal product in urgent situations such as ''in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.'' The wording of Article 5 of Directive 2001/83/EC[1] is not precise and does not mean to specify the conditions for authorization of such medicinal products but, rather, gives EU Member States the authority to allow such exceptions. Of note, only medicinal products administered to individual patients under the direct responsibility of the physician was foreseen.

In 2004, the Regulation 726/2004/EC[2] officially used for the first time the term ''compassionate use programme'' and included provision for the use of an unauthorized medicinal product in a group of patients. Recital 33 of this Regulation, although not legally binding, promotes a common approach regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation throughout the EU. Article 83 of Regulation 726/2004/EC[2] specifically foresees the possibility of obtaining an opinion from the European Medicines Agency (EMA) on the conditions for use and distribution, as well as patients targeted in a proposed CUP. It also requires the Member States to take into account the 'opinion' for a product (if available) if they intend to allow such a CUP. One further step was taken with the publication of an EU Guideline[3] in 2007 (referred in the rest of this article as the 'EU CUP Guideline'). The EU CUP Guideline clarifies the criteria of CUP eligibility for centralized products and provides details on the procedure for obtaining the EMA opinion on a CUP. However, the EU CUP Guideline only proposes the possibility for Member States to obtain an opinion from the EMA on a CUP, but the CUP approval remains national, i.e. made by the Member States (see Section 2.2).

Overall, although general principles of CUPs are laid out in the EU regulatory texts, they are considered as 'soft' laws and the wording used is relatively vague. There is no single EU-wide regulatory harmonized framework. Effectively, the individual national Member State laws on CUPs, where they exist, prevail and are considered as 'hard' laws.

1.2 General Principles

The primary objective of a CUP is to provide severely ill patients with early access to important and/or innovative medicinal products. A CUP is distinct from a clinical trial and, strictly, cannot be used for investigational purposes or commercial preauthorization activities. Promotion of the medicinal product under a CUP or the CUP itself is not permitted. Generally, a CUP is conducted in parallel to clinical trials with the medicinal product or to the evaluation of a marketing authorization application (MAA) by the competent authority.

A CUP is usually granted as an exceptional and temporary measure, when the following conditions are met:

- The product is for the treatment, prevention or diagnosis of a serious or rare disease.
- There is an absence of a suitable therapeutic alternative (medicinal product or other) available in the concerned country.
- The benefit/risk ratio of the medicinal product is presumed to be positive.

When competent authorities assess a CUP application the following principles are considered:

- A patient proposed to be included in a CUP did not meet the criteria for inclusion in any corresponding clinical trials.
- The granting of the CUP will not delay ongoing clinical trials, which alone are intended to provide precise and essential information about the benefit/risk ratio of a medicinal product.
- The CUP is not be intended to collect supportive data for a MAA and does not have any investigational objective.
- The CUP is not to be used to continue a patient's treatment initiated in the context of a clinical trial. For this particular purpose, it is advisable to extend the clinical trial concerned by an amendment to the initial protocol.

CUPs can be divided into the following two major types:

- Named patient compassionate use programmes (NP-CUPs): the physician requests a CUP authorization for a single identified patient. The approval is then granted for this single patient for a limited time.
- Cohort compassionate use programmes (Coh-CUPs): the physician or the company requests a CUP authorization for a group of patients or a hospital site. The approval is then granted for a defined group of patients, for a limited time.

As highlighted in table I, not all EU Member States allow both types of CUP and there are significant differences in the regulatory requirements between Member States. For a matter of simplicity, we will only use the terms NP-CUP and Coh-CUP in this article, although there are other ways to refer to these programmes.

2. Regulatory Procedures

2.1 Named Patient Compassionate Use Programme (NP-CUP)

Article 5 of Directive 2001/83EC[1] states that "A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility."

In general, the patient's physician makes the initial request for a NP-CUP authorization to the regulatory authority based on available information concerning the medicinal product. This information may include evidence on the quality, safety and efficacy of the medicinal product drawn from the investigational medicinal product dossier, the investigator's brochure, a bibliography and/or the (draft) summary of product characteristics.

After the Authority reviews the dossier, the authorization is issued to the physician. The pharmaceutical company developing the product must decide whether to supply the product and is responsible for shipping the product to the site. The treating physician is then responsible for reporting any serious adverse reactions (SARs) to the Authority. The company can request that the reporting physician informs them of such SARs, but cannot force this 'double' reporting.

In order to be able to properly manage named patient requests, particularly if they have come from different countries, it is advisable that the drug manufacturer defines internally specific and uniform eligibility criteria for patients to ensure appropriate and safe use of the medicinal product. This would help to avoid ethical dilemmas, and ensure a fair and consistent response to all requesting physicians.

A NP-CUP does not usually require intensive interaction with the Authority and, therefore, the pharmaceutical company has a relatively light administrative burden. The Authority's approval process for individual requests is precedence based and is usually rapid.

2.2 Cohort Compassionate Use Programme (Coh-CUP)

The Article 83 of Regulation (EC) No 726/2004[2] foresees the possibility of "making a medicinal product [...] available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product."

In most cases, pharmaceutical companies are required to prepare and submit a regulatory dossier to the Authority in order to obtain authorization for a Coh-CUP. In a few cases, such as in Italy, this dossier has to be prepared and submitted by a group of physicians. Then, after obtaining authorization from the Authority, the company will communicate carefully on the availability of a Coh-CUP to patients. The treating physicians then send requests to the pharmaceutical company to participate in the Coh-CUP. If the company approves participation, it is responsible for shipping the product to the physicians.

As a first step, the pharmaceutical company should develop a specific protocol that includes patient inclusion criteria, instructions on how the product should be used, along with the corresponding safety monitoring and pharmacovigilance procedures. The protocol provides a foundation for a publicly available homogeneous rule for patient acceptance and treatment within the programme.

Coh-CUPs are usually set up close to the MAA submission date, usually when phase III data are available. In fact, in some Member States (e.g. France), it is mandatory to wait for this time point. However, in certain conditions, medicinal products in phase II may also be eligible for Coh-CUP. The approval procedure is usually longer than for NP-CUPs, as a large amount of data is considered and the responsibility for approval is typically with the national Authority. Moreover, the volume of product available for supply for the CUP will be considered by the authorities. Often the pharmaceutical company will need to provide a commitment on the amount that can be supplied.

A successful Coh-CUP requires a close relationship with the regulatory authority and inevitably there will be a substantial administrative burden for the pharmaceutical company.

Table I. Overview of compassionate use programmes (CUPs) in selected EU countries

Country	CUP type	Regulatory procedure	Review times	Import license	Payer	Legal basis
France	Both	Well defined	NP-CUP: rapid (24–48 h if already evaluated by AFSSAPS); Coh-CUP: 2–4 mo	NP-CUP: CUP authorization taken as import permit; Coh-CUP: import permit needed	Hospital or national health insurance	Code de la Santé Publique (Art. L.5121-12 and R.5121-68 to R.5121-76)
Denmark	Both	Well defined	Within 3–4 wk	Imported by pharmacy	Hospital/patient co-payment Reimbursement as for approved products	Lov om lægemidler no. 1180 as last amended 17 June 2008
Germany	Both	Very recent and currently under change[a]; managed by local supervizing authorities	2–3 mo	Import permit required	Company	14 AMG Novelle and 15 AMG Novelle
Italy	Both	Well defined but complex, needs local expertise	NP-CUP: 1 mo; Coh-CUP: 3–9 mo	Ethics committee written approval required	Hospital or national health insurance	DECRETO 8 maggio 2003; Legge 648/1996
The Netherlands	Both	Well defined for NP-CUP; very recent for Coh-CUP	NP-CUP: within 4 wk; Coh-CUP: no defined timelines	Import permit required	Patient/company usually not reimbursed	Art. 40.3.c Geneesmiddelenwet van 8 Februari 2007 Art. 3.17.1 Regeling Geneesmiddelenwet van 25 Juni 2007 Circular 2002-06-IGZ
Spain	Both	Need local expertise; Coh-CUP newly authorized by Royal Decree 1015/2009	Very variable, case by case	Need to apply for importation to the AEMPS	Company	Real Decreto 1015/2009; Ley 29/2006 (Art. 24) and Real Decreto 223/2004 (Art. 28)
UK (under change[b])	NP-CUP ('Specials'[c])	Well defined	4 wk after receipt of notification of intent to import	Import permit required (allow at least 6 wk)	Reimbursement case by case, price can be set freely	SI1994 no. 3144

a The CUP system in Germany is becoming more defined. Following on from the 15th Amendment of the German Drug Law, which came into force in July 2009, the Ordinance is expected to be released soon.

b Note that the UK is putting in place a more defined framework for unauthorized medicinal products, which can bring significant potential benefits for patients for whom there are currently no, or very limited, treatment options available. The MISG released a report presenting the key elements of this scheme. The MHRA undertook consultation and the scheme should be finalized later in 2010. As of 23 July 2010 it has not been released yet.

c 'Specials' is the term used by the UK regulatory agency (MHRA) for unlicensed medicinal products exempted from authorization for individual patients.

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; **AFSSAPS** = Agence Francaise de Securite Sanitaire des Produits de Sante; **AMG** = ArzneimittelGesetz; **Art.** = article; **Coh-CUP** = cohort compassionate use programme; **IGZ** = the Netherlands Health Care Inspectorate; **L** = Législative; **MHRA** = Medicines and Healthcare products Regulatory Agency; **MISG** = Ministerial Industry Strategy Group; **NP-CUP** = named patient compassionate use programme; **R** = Réglementaire; **SI** = statutory instrument.

2.3 Conclusions for NP-CUP and Coh-CUP

Table II summarizes the main differences between a NP-CUP and a Coh-CUP. It should be noted that in some Member States hybrid programmes exist where the distinctions between a NP-CUP and a Coh-CUP are not as pronounced. For example, in France the 'ATU nominative Protocole d'Utilisation Thérapeutique' is a named-patient programme that requires a defined protocol similar to that of a Coh-CUP or a clinical trial.

NP-CUP is less burdensome and more flexible but pharmaceutical companies have little control on the use of their medicinal product in this context. When multiple requests from physicians and strong involvement from patient organizations are anticipated, it is recommended that pharmaceutical companies consider establishing a Coh-CUP programme.

2.4 Comparison of CUPs in Selected EU Member States

Table I provides an overview of the existing compassionate use programmes in selected EU Member States and highlights the differences between those countries.

In practice, the regulatory framework and management of CUPs are very different from one EU country to another, i.e. the eligibility conditions, regulatory procedure and review times vary greatly between the Member States. Such factors must be investigated and be well understood when developing a CUP strategy.

2.5 Opinion from the European Medicines Agency

As mentioned in Section 1.1, for medicinal products eligible for marketing approval via the centralized procedure, the national authority of a Member State receiving a CUP request can request an opinion from the EMA. In this context, the EMA provides recommendations on (i) the conditions of use; (ii) the conditions for distribution; and (iii) the targeted patients in the CUP in a given therapeutic indication.

The EMA's opinion on a CUP can be applicable for all Member States throughout the EU. However, the Member States are not bound to follow the EMA's recommendations because approval of the CUP remains a national responsibility.

As of 19 March 2010, the EMA has publicly released their 'opinion' on the two first CUPs. The first CUP opinion was for intravenous Tamiflu® (oseltamivir) in January 2010[4] after a request from the Finnish Agency in October 2009. The second CUP opinion was for intravenous zanamivir in February 2010[5] after a request from the Norwegian Agency in November 2009. Both medicinal products are for the treatment of serious conditions related to H1N1 influenza virus or seasonal flu.

3. Points to Consider Before Implementing CUPs in the EU

We present several points for companies to consider when making 'go/no go' decisions on CUPs.

3.1 Pharmacovigilance

In accordance with Volume 9A of the Notice to Applicants,[6] when establishing a CUP, pharmaceutical companies should be aware of their pharmacovigilance responsibilities, in particular:

- Compassionate or named-patient use of a medicine should be strictly controlled by the company responsible for providing the medicine and should ideally be the subject of a protocol.
- Such a protocol should ensure that the patient is registered and adequately informed about the nature of the medicine

Table II. Comparison of the named patient compassionate use programme (NP-CUP) and the cohort compassionate use programme (Coh-CUP)

Critical issues	NP-CUP	Coh-CUP
General	Not a predefined programme; may be difficult to handle diverse requests from multiple sources, especially for a small pharmaceutical company	Predefined programme by the pharmaceutical company and agreed upon with regulators
Cost/resources needed	Low cost; if imported, there is generally no need for a permit	High cost (preparation of formal dossier and import permit request, patient follow-up and often mandatory pharmacovigilance reporting to agencies)
Patients to be treated	Typically <50 patients	Up to several hundred patients
Regulatory procedure	Multiple, individual requests from physicians	Application dossier usually from pharmaceutical company
Liabilities	Prescribing physician	Pharmaceutical company
Review time	Within a few weeks for first case, and a few days for subsequent cases in one country	Can take several months

and that both the prescriber and the patient are provided with the available information on the properties of the medicine with the aim of maximizing the likelihood of safe use. The protocol should encourage the prescriber to report any adverse reactions to the company, and to the competent authority, where required nationally.

- Companies should continuously monitor the benefit/risk balance of medicines used on a compassionate or named-patient basis (subject to protocol or not) and follow the requirements for reporting to the appropriate competent authorities. As a minimum, the requirements laid down in Chapter I.4, Section 1 of Volume 9A on individual case safety reports (ICRS) apply.

Frequently, the pharmaceutical company will be responsible for pharmacovigilance during a CUP, which includes the identification of a pharmacovigilance responsible person.

3.2 Financing a CUP

Often, there are no Authority fees for a CUP application, as they are generally made by physicians. Depending on the national legislation, the medicinal product is provided to the patients free of charge, or the pharmaceutical company can charge for it with the cost payable by the patient, hospital or national health insurance system.

The payment of such products can be a major consideration, especially in countries where national health insurance reimburses the product. In some countries, such as in France, the price of a medicinal product established in a CUP will influence future price negotiations after the medicinal product is granted marketing authorization, as well as the timing of these negotiations. In such cases, it can be difficult to obtain a higher price than was applied in the CUP and it is wise to conduct pharmacoeconomic studies prior to proposing the price for the product during the CUP. Significant financial resources will be required for the management, logistics, follow-up, tracking and safety reporting during the CUP.

3.3 Human Resources

Regardless of whether the pharmaceutical company intends to establish either a NP-CUP or Coh-CUP, it is anticipated that the following resources will be needed:

- A project manager with support from the chief medical officer.
- Internal regulatory support for submissions.
- Internal pharmacovigilance support for reporting safety events, i.e. a pharmacovigilance-responsible person.
- Feedback on price and reimbursement advisors for setting price.
- An importer and distributor.

The project manager will have a central role since he/she must manage a complex channel of communication, i.e. interact with physicians, national agencies, pharmacies and sometimes with patients.

The importer and distributor roles are also very important; ideally, they should be performed by an organization with prior experience in CUPs.

3.4 Selection of Member States

Although there are EU-wide general principles on CUPs, initiation of a CUP in the EU requires national Member State Authority approval and must be conducted in accordance with national Member State legislation that is far from harmonized. As when planning clinical trial programmes in the EU, national requirements should be considered carefully before initiation of a CUP in any Member State, mostly for Coh-CUP. National factors to consider include the following:

- Availability of CUP regulatory framework – NP-CUP, Coh-CUP or both.
- Definition/transparency/complexity of the regulatory procedure.
- Review time.
- Need for an import license, which may extend considerably the start of the CUP.
- Pricing strategy: how the price will be determined and who will be the payer.

Frequently, the potential number of patients in a Member State that can be treated under a CUP is also a key consideration.

3.5 Additional Considerations Specific to Medicinal Product/Disease

Before considering setting up a CUP, pharmaceutical companies should have a good understanding of whether the national regulations are well defined and favourable or not; however, there are additional criteria, such as disease and product-dependant issues, to be considered on a case-by-case basis as follows:

- Evaluation of key opinion leaders' support/interest in the medicinal product. However, pharmaceutical companies should be extremely careful regarding communication. It is strictly prohibited to advertise unauthorized medicinal products in the EU and it may be difficult to draw the line between awareness and advertising programmes.
- Public perception.
- Unmet medical need. The availability of a medicinal product in a NP-CUP or Coh-CUP in some EU countries can trigger

requests from other EU authorities to conduct the programme in their own territory.

Although these criteria are less tangible, they are no less important than the regulatory criteria and, if overlooked, will not only threaten the success of the CUP but also the future marketing of the product.

4. Conclusions

There is no single, centralized EU-wide procedure for CUPs. General EU-wide principles apply but the initiation of a CUP in the EU requires national Member State Authority approval and must be conducted in accordance with national Member State legislation that is far from harmonized.

Before evaluating whether a medicinal product is eligible for compassionate use in the EU, several criteria have to be taken into account but, above all, the local physicians need to be the driving force. The targeted disease must represent an unmet medical need and be a serious or life-threatening condition. The product must also be associated with a presumed high positive-benefit/risk ratio.

Coh-CUPs not only bring significant benefits to patients 'early', but may also accelerate the launch of the products in certain countries in the EU and in certain cases bring the first revenues to companies developing the medicinal product. Successful Coh-CUPs will raise the general awareness of the product in Europe.

However, in order for these CUPs to be successful, they need to be well controlled, and risks carefully anticipated, particularly regarding safety aspects. Finally, patients' expectations in some countries where the product is not available may become overwhelming for some companies and can impact negatively on the company's public profile. Careful planning for a CUP is critical, and should take into account the perspective of both treating physicians and patients, as well as the national regulatory frameworks.

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