COMPARISON OF EARLY ACCESS PROGRAMS FOR ORPHAN DRUGS IN THE EU-5 COUNTRIES

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OBJECTIVE:

- There are several mechanisms other than Health Technology Appraisal (HTA) approvals and Pricing & Reimbursement (P&R) decisions by which patients can access orphan drugs pre-launch within a local healthcare system.
- Early access programs (EAPs) for orphan drugs differ among the EU member states due to their national regulation based on which the EAPs are implemented.
- The objective of this analysis is to examine similarities and differences of EAPs in the EU-5 countries (Germany, France, Italy, Spain and UK).

METHODS:

- Data was retrieved by conducting targeted literature searches including relevant institutional websites, national laws and regulations.

RESULTS:

- Two types of EAPs exist in all five EU countries: (1) Compassionate use programmes [CUP; synonyms: “cohort Temporary Authorisation of Use” (ATU), France; Early Access to Medicines Scheme (EAMS), UK] which are put in place and requested/funded by marketing authorization holders for a group/cohort of patients of a hospital. (2) Individual patient funding requests [Named Patient Program, NPP; synonyms: “nominative ATU”, France; “Individual Funding Request” (IFR) UK] which are granted in response to individual requests by physicians/hospitals on behalf of named patients.
- Table 1 depicts similarities and differences between the two types of EAPs, CUPs and NPPs.

Table 1: Comparison of CUP and NPP in the EU

Criteria	CUP (EU)	NPP (EU)
Legislation in place	Article 83 (1) of Regulation (EC) No 726/2004	Article 5 of Directive 2001/83/EC
Who initiates the program?	Manufacturer/Group of physicians (e.g. in Italy)	Physician
Criteria to define/select target population is set by…	National regulatory agencies	Manufacturer/Physician
Who can benefit from program? Limitation in use?	Group of patients i.e. more than one (permission is granted to a clinic or hospital as opposed to a particular patient)	Only named patients for whom physician has made a request
Liability	Manufacturer	Prescribing physicians/hospitals
Medicinal product should be undergoing clinical trials or awaiting market authorization?	✓	✕
Is off-label use permitted?	✕	✓
Are physicians paid for taking part in the program?	✕	✕
Are drugs in program priced?	✓ (possible)	✓ (possible)

Source: Patil, 2016; Yazdanie, Boggio Francesca: Initiating early access programs in Europe: Five things to consider.
NPP: Named patient program; CUP: Compassionate use program

- Table 2 shows details of CUPs in Germany which were initiated in July 2010. Today, there are 10 cohort CPUs, 50 % of them in oncology. While the process for the cohort program is more complex than the NPP, it grants the manufacturer a higher degree of control such as limiting the medication to a particular patient subgroup.
- Products entering CUPs are not funded in Germany.

Table 2: Overview of existing EAPs in Germany

Type	Individual patients	Groups/cohorts of patients
Agencies responsible	German Federal Institute for Drugs and Medical Devices (BfArM) and The Paul-Ehrlich Institute (PEI)	
Initiator	Treating physician	Manufacturer/license holder
Duration	Up to 1 year with possibility of renewal until commercial drug availability	
Pricing and Reimbursement	Product supplied free of charge	
Restrictions and requirements	- Patients should enroll in clinical trials, where possible	- The drug has to be subjected to clinical trials in Germany or abroad - Must be able to show product’s safety and suspected efficacy, medical need and urgency, as well as provide justification as to why patients cannot be included in clinical trials

Source: Federal Institute for Drugs and Medical Devices, 2020

- Table 3 shows details of CUPs in France. The Temporary Utilization Program (ATU) has been in place since 1994 in France. In 2018, there were 20 new cohort ATUs, and 217 new medicines were available through named-patient ATUs.
- In 2018, 15.987 patients have been included in a named patient ATU and 5.642 have been newly included in a cohort ATU program.
- Reimbursement opportunities make CPUs in France potentially the most attractive in Europe.
- Products entering CPUs are funded in France, where the company fixes the compensation until the price negotiation.
  - If the mean cost per patient is higher than ten thousand euros per year and the turnover is higher than thirty million euros for the year, the pharmaceutical company will have to repay the difference between 10.000 € and the real cost.
- After obtaining the market authorization and a public price published in the French official journal, the company will have to repay the difference between the public compensation declared under ATU by the company and the negotiated price.

Table 3: Overview of existing EAPs in France

Type	Individual patients (Nominative ATU)	Groups/cohorts of patients
Agencies responsible	French National Agency for Medicines and Health Products Safety (ANSM)	
Initiator	Prescribing physician	Manufacturer/license holder
Duration	1 year, renewal is possible (renewal application to be submitted at least 2 months before ATU expiration)	
Pricing and Reimbursement	- Free pricing and full reimbursement - Difference with price negotiated at launch has to be paid back (fines are possible if the difference is significant)	
Restrictions and requirements	- Rare or serious diseases with no satisfactory alternatives available in France - MA application submitted or engagement to submit an application at a pre-specified date	
	- Efficacy and safety for the patient are presumed	- Efficacy and safety for the patient are presumed - Adverse event reporting required

Table 4: Number of cohort ATU and named patient ATU per year in France

	2014	2015	2016	2017	2018
Cohort ATU program					
New drugs in a cohort ATU program	25	13	10	11	20
Drugs in cohort ATU program which obtained a marketing authorization	24	12	9	8	16
Newly included patients	12.111	10.216	11.909	8.250	5.642
Named patients ATU					
Named-patients ATU	25.521	24.791	27.095	22.295	21.633
Medicines available under named patient ATU	208	219	205	253	217
Patients included	18.831	17.829	19.625	16.621	15.987

Source: ANSM, 2019; Ansm Annual Report, 2018.

- Table 5 shows details of CPUs in the UK. The Early Access to Medicines Scheme (EAMS) program was launched in 2014 in the UK, and by today, a total of 27 programs have been approved. The application process for manufacturers requires submission of a dossier with the latest available data, and evidence requirements for both regulatory purposes and NICE appraisal, thus potentially contributing to the data required for MA application and subsequent appraisal.
- Products entering CPUs are not publicly funded in the UK.
- Additionally, an alternative program can grant access to centrally licensed but not yet reimbursed drugs.
- Commissioning through Evaluation (CeT) can grant access to non-reimbursed products in order to facilitate data collection. Access is also possible through Individual Funding Requests (IFRs) post-marketing authorisation, but this route is used increasingly less frequently.

Table 5: Overview of existing EAPs in the UK

	Individual Funding Request	Early Access to Medicines Scheme
Type	Individual patients	Groups/cohorts of patients
Agencies responsible	Medicines and Healthcare products Regulatory Agency (MHRA) is reponsible for the benefit/risk scientific opinion; National Institute for Health and Care Excellence (NICE)	
Initiator	Prescribing physician	Manufacturer/license holder
Duration	Usually ends once the medicine receives a product license	12-18 months with 3 monthly review
Pricing and Reimbursement	Product supplied free of charge	
Restrictions and requirements	- The product is likely to offer benefit or significant advantage over and above existing options - Potential adverse events are likely to be outweighed by benefits	
	- Although the company will record what they supply, there is often no central register for the patients that are being treated	- The applicant is able to supply the product in each region in the UK

Source: Medicines and Healthcare products Regulatory Agency, 2019.

Table 6 shows details of EAPs in Italy. The Italian Medicines Agency (AIFA) defined different tools to grant Italian patients with an early access to important drugs.

- Law 326: through this law AIFA established also a specific fund (Fondo AIFA 5%) for the reimbursement of orphan and lifesaving drugs awaiting market entry.
- Law 648/96: the law is dedicated to important drugs authorized abroad, drugs still under clinical evaluation and drugs used “off label”. The request for inclusion into the 648/96 list (as well as Fondo AIFA 5%) shall be submitted by the Italian Scientific Community to the CTS AIFA which performs its evaluation and publishes a positive/negative decision (i.e. positive shall mean a complete reimbursement by the AIFA).
- Cnn class: by the so-called Balduzzi Decree, AIFA is required to grant a MA promptly after EMA’s approval, listing drugs, within 60 days after EMA approval in a newly defined Cnn class where «C» stands for not reimbursed and «nn» stands for not negotiated. Once the product is classified in the Cnn class the company is allowed to start the commercialization immediately after the Cnn class publication in the Official Journal (GURI) by just communicating the (freely set) price as well as the date of first marketing of the product (without waiting for the outcomes of the pricing negotiations with the AIFA).
- Compassionate use: treatment option that allows the use of investigational drugs in patients with severe diseases. This Law has been designed for patients who have no other satisfactory treatment available to them.

Table 6: Overview of existing EAPs in Italy

	L 326	L 648/96	Cnn Class	CPU
Type	Individual patients	Groups/cohorts of patients		
Agencies responsible	AIFA – Agenzia Italiana del Farmaco			
Initiator	Prescribing physician		Manufacturer/license holder	
Duration	Until end of patient’s treatment	Until commercial drug availability	Until P&R Decree publication	Until commercial drug availability
Pricing and Reimbursement	Free pricing and full reimbursement		Free pricing and to be paid by patients of hospital	Product supplied free of charge
Restrictions and requirements	Only if an unmet medical need		European authorization needed	Has at least to be subjected to clinical trials or approved abroad

Source: Agenzia Italiana del Farmaco (AIFA), 2019.

- Table 7 shows details of CPUs in Spain. Non-authorized medicines are available in Spain under the regulation 1015/2009. This regulation covers access to medicines in special situations: compassionate use, off-label use of medicines and foreign medicines.
- Products entering CPUs are usually not publicly funded in Spain (before EU Marketing authorization).
- Additionally, an alternative programe can grant access to centrally licensed but not yet reimbursed drugs.
- The price for approved but not yet reimbursed products (P&R negotiation is ongoing) is freely set (in most cases) with a repayment of the difference between the charged and final negotiated price once the national reimbursed price is in place.

Table 7: Overview of existing EAPs in Spain

Type	Individual patients (Named patient basis)	Collective (Authorization of use)
Agencies responsible	Spanish Agency of Medicines and Medical Devices (AEMPS)	
Initiator	Prescribing hospital	AEMPS
Duration	Until commercial drug availability	
Pricing and Reimbursement	- Before EU marketing authorization (MA): free of charge - Between MA and Price P&R: usually reimbursed	
Restrictions and requirements	- Severe or debilitating disease - Unmet medical need - Hospital setting only - Not taking part in a clinical trial - Collection of safety information necessary	

Source: Spanish Agency of Medicines and Medical Devices (AEMPS), 2019.

CONCLUSIONS:

- There exist two types of EAPs across all five EU-5 countries.
- EAPs are country-specific, and products entering these programs are generally not paid for, except in France and Italy where dedicated payment can be granted.

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