Early Access Pathways

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There is growing demand for early access to medicines

Over the past few decades, there has been growing demand for early access to medicines that treat serious or life threatening diseases, for which there are minimal alternative treatment options.

Four key drivers for early access:

• regulatory and reimbursement delays resulting in wide variation in access timelines between different countries

• increased collaboration with academic groups

• patient pressures, with advocacy groups gaining increased influence within regulatory and Health Technology Assessment (HTA) processes

• emerging health threats.
Based on these pressures, some countries have introduced new options and/or processes to speed up access to medicines.

- This includes access before marketing authorization (MA), speeding up the MA, or less often, the HTA processes
- The approach of each country differs, leaving patients, clinicians, and companies navigating a myriad set of rules and processes
- All approaches are focused on access for serious and/or life threatening diseases where significant unmet clinical need remains
- Approaches differ in whether companies are required to provide therapies free of charge, or if the government provides reimbursement during the early access period
- Many newer initiatives emphasize early dialogue with multiple stakeholders and an expanded toolbox for evidence generation, including real world studies
The EMA has several different early access programs

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<th>EARLY ACCESS ROUTE</th>
<th>CONDITIONS</th>
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<td>Accelerated approval</td>
<td>Reduced CHMP/CAT assessment time for potentially innovative products; 150 days instead of 210 days</td>
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<td>Compassionate use</td>
<td>Access to unauthorized drugs targeting patients with life threatening or serious debilitating diseases, for which there are no available alternatives, can be allowed by EU member states</td>
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<td>Hospital exemption</td>
<td>A permission that can be granted by EU member states for unauthorized ATMPs to be used on a named patient basis in a hospital setting within the same member state only and under the exclusive responsibility of the treating physician</td>
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<tr>
<td>Conditional approval</td>
<td>Accelerated EMA approval for therapies fulfilling a significant unmet need prior to the availability of mature clinical trial data. The authorization is valid for one year and can be renewed once longer term and supportive clinical data become available</td>
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<td>PRIME</td>
<td>Drugs determined to be “PRIority MEdicines” benefit from early scientific advice and eligibility for an accelerated assessment</td>
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**ATMP** = advanced therapy medicinal product; **CAT** = Committee for Advanced Therapies; **CHMP** = Committee for Medicinal Products for Human Use; **EMA** = European Medicines Agency

Source: Elsanhoury et al., 2017
PRImority MEdicines scheme (PRIME)

PRIME was introduced by the EMA in March 2016 as an initiative to accelerate access to drugs that may provide a major therapeutic advantage over existing treatments, or benefit patients with no treatments.

Eligibility for PRIME:

- addresses a significant public health need
- demonstrates a high level of therapeutic innovation
- supported by strong preclinical efficacy and tolerability data

Note: Eligibility criteria are somewhat relaxed for therapeutics stemming from SMEs or academia, with entry possible prior to the collection of human tolerance data. However, supportive clinical data are likely to significantly enhance the chances of gaining PRIME designation.

Source: EMA, 2019a
PRIority MEdicines scheme (PRIME)

Major benefits include:

- Early appointment of a CHMP or CAT rapporteur to provide guidance and support for the MA process
- A kick off meeting with rapporteur and other clinical/regulatory experts to understand the development plan and gain early guidance on the requirements for MA
- Scientific advice from the EMA helping to ensure optimal clinical trial development, supporting a regulatory approval, and optimizing the use of limited resources
- The potential for an accelerated assessment (150 days) at the time of MA application
- SMEs can also be eligible for a filing fee reduction

Source: EMA, 2019a
The Temporary Authorization for Use (ATU) scheme has been available since 1994, with the aim of providing early access (prior to MA) to new promising medicines where there is a genuine public health need.

ATUs are issued by the National Agency for the Safety of Medicines and Health Products, and are granted subject to meeting three conditions:

- treatment of a serious or rare disease
- absence of a suitable therapeutic alternative in France
- presumed positive benefit/risk ratio.

**Note:** Patients should be considered for clinical trials before being offered a therapy under the ATU process, as expanded access through the clinical trial process is preferred by the regulatory agency.
Costs associated with the ATU scheme rose significantly during 2012-16:

- spending on ATU drugs rose from just over €35m ($40.6m) to more than €470m ($544.7m)
- the number of ATU drugs prescribed increased from 190 to more than 480
- the number of drugs with ATU authorizations rose from 105 to 148

Rising spend prompted accusations that the ATU scheme was being abused by pharmaceutical companies.

Source: Sam et al., 2017
There are two methods of obtaining early access in Italy

**Compassionate use** (most commonly utilized)

**Law 648** (utilized in more exceptional cases)

### Compassionate Use

- When there is no [licensed] therapeutic alternative, the patient has a serious or rare disease, or where the patient cannot enter a clinical trial
- Drugs provided free of charge
- Requests must come from physicians, for named patients
- AIFA ethics committee plays a pivotal role in the decision making process

### Law 648

- Sets out a list of non authorized therapies which may be supplied under certain conditions
- Drugs can be listed if there are no therapeutic alternatives, and the drug has MA in other markets / is being investigated in trials but is not yet authorized / the product use is for a population other than the one authorized in Italy
- Companies are paid market price

Source: Covington, 2017
New legislation regarding early access introduced in 2017

- Expanded access programs intended to treat orphan or rare diseases can now be requested based on results from Phase I clinical trials (previously it was required that Phase III trials were ongoing, or Phase II/III trials were already completed).

- Expanded access can be requested for therapies without MA, or with an MA in a different patient population. In addition, access can also be requested for ATMPs.

- The introduction of a new submission process in which physicians submit a request to the Ethics Committee only, with an opinion then issued electronically to AIFA within three days of the opinion date.

Furthermore, in January 2017, an important advisory opinion was adopted, enabling patients to be enrolled in a compassionate use program or supplied with a medicine listed in the 648 List after the drug has gained MA, at least until the company starts to commercialize it in Italy.

As there is often a significant delay between MA and national reimbursement, this amendment attempts to prevent fragmented patient access to potentially innovative treatments while reimbursement is being secured.

Source: Covington, 2017
The Early Access to Medicines Scheme (EAMS) was introduced in April 2014, with the aim of providing access to innovative treatments prior to a full MA.

- Typically for therapies which have completed Phase III clinical trial programs (although exceptions are sometimes made for Phase II products, dependent on sufficient safety and efficacy data).

- Voluntary program for manufacturing companies.

- Sits alongside the routine licensing procedure for drugs in the UK.

In theory, products with a positive EAMS opinion could be available to NHS patients 12–18 months before MA is granted.

Source: EAMS, 2019
PIM designation — stakeholder comments

“...it is a sign potentially to investors that this is not just a bright idea, it is not just a wish, a fantasy that hopefully will be fulfilled, but it has the sort of imprint of the regulatory agency, and as thinking yes, this is an idea with legs.”

Alastair Kent, Genetic Alliance

“...the PIM offers companies a kind of flag so the regulatory system thinks that their molecule/ indication is important, it is innovative, it can meet an unmet medical need potentially, there is a review of the data and it is something that they can publish and put out into the pharma press and put out into the harma press and elsewhere...”

Medical Assessor, MHRA

“PIM offers an earlier interaction with other stakeholders in the UK... four NHS systems, and also the HTA bodies, and these contacts can be very useful in terms of the companies engaging earlier with these other relevant stakeholders for patient access, not only for EAMS, but also for more longer term, in terms of once the MA has been granted.”

Alastair Kent, Genetic Alliance

To download the full report Early Access to Medicines in the US and Europe, go to: https://service.datamonitorhealthcare.com/strategy/market-access-insights/insights/article206612.ece