

EARLY ACCESS FOR ORPHAN DRUGS: NEED FOR AN INTEGRATED APPROACH

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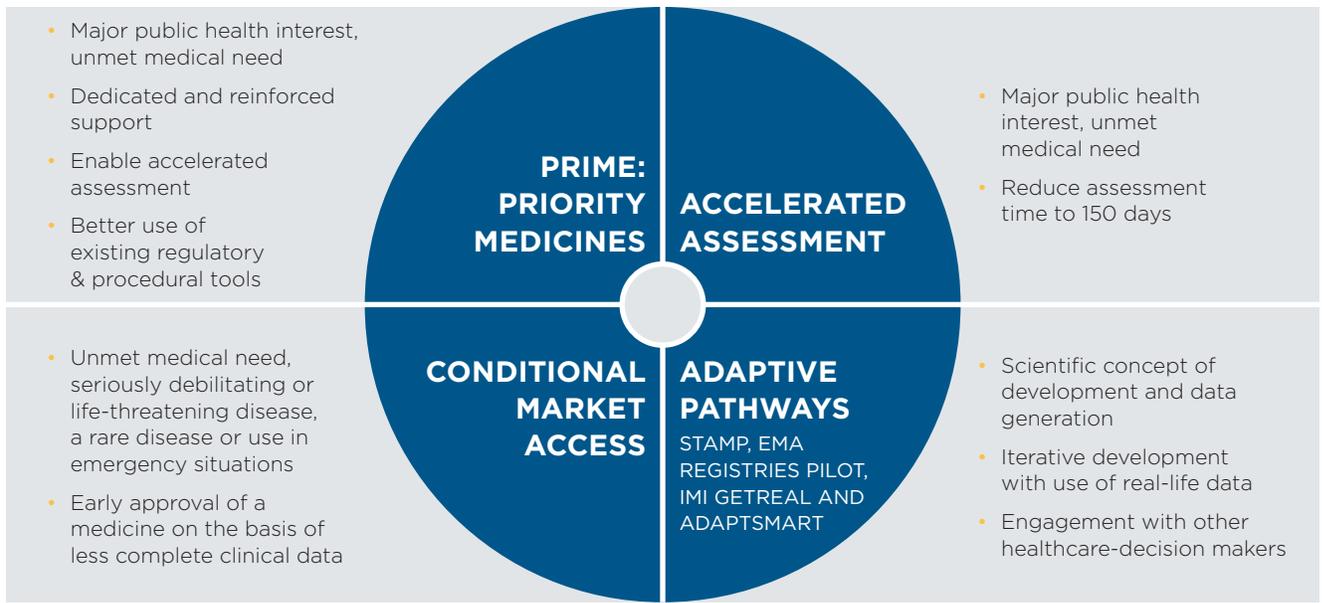
Rare diseases exert a global public health burden in both severity of their manifestations and total number of people they afflict. For patients, considerable barriers exist in terms of access to appropriate diagnosis, care and limited or non-existing treatment options. Regulators and HTA bodies/payers have recognized that paradigms of drug development (such as randomized clinical trials (RCTs), which are feasible for common diseases, may not be feasible for rare diseases. Transformative orphan, specialty and advanced therapeutics often defy traditional regulatory and access routes, potentially denying patients safe and effective treatments.

Early access pathways are evolving, requiring multiple stakeholder interactions (including regulators, HTA bodies/payers and patient groups) with the aim to facilitate and accelerate development, marketing authorization and access of medicines to patients in areas of high unmet needs. To achieve true early access, an integrated approach is required, addressing multiple stakeholders' needs (positive benefit-risks for regulators, value-for-money/affordability for payers, commercial viability for industry), these initiatives emphasize early dialogues, a

flexible development life-cycle plan, and an expanded toolbox for evidence generation, with pragmatic and real-world studies complementing RCTs. Orphan drug designation is not an early access tool per se, and orphan medicines do not automatically qualify for accelerated procedures. Nevertheless, orphan drugs are highly likely to be eligible for early access. Therefore, the feasibility of orphan designation should be considered as part of any early access strategy.

Evolution of early access pathways

Various early access paradigms now exist, utilizing legal tools and initiatives with the aim to foster patients' timely access to medicinal products that address unmet medical needs. The increased regulatory and HTA bodies/payers' focus on accelerated development pathways offers interesting opportunities for prospective market authorization and more rapid market access. The regulators and HTA bodies/payers are challenged with finding the appropriate balance between the need for rapid access to novel, promising drugs whilst ensuring comprehensive data on their benefits, risks and value. This is not a new situation, and has been made more prominent by high-profile drug withdrawals and conflicting demands of various stakeholders. There are additional hurdles for orphan drugs in that they differ from conventional medicines as they are used to treat rare conditions for which there may be no alternative treatments available (therefore no



appropriate comparators) and orphan drugs tend to target life-threatening and chronic diseases. Also, assessing the benefit-risk balance can be a challenging process involving the evaluation of complex, or even controversial, sets of data (especially if those data sets are from small and/or special populations). To help address these challenges, regulators and HTA bodies have collaborated to develop various early access paradigms with the aim of achieving better patient access to important medicines.

Schemes and tools

The EMA adaptive pathways pilot very much targeted towards the patient, involving all stakeholders. Whereas, the new EMA Priority Medicines (PRIME) scheme is regulatory-focused, with the aim to simplify and guide companies developing innovative medicines for unmet need.

Components of PRIME were assembled, namely advice from HTA bodies and payers, trying to use other data sources, not only from RCTs, but also registries, real world data (RWD), etc. PRIME pulls all these aspects together, without any new legislation. The features of PRIME are intended to create a toolbox attractive to all companies, navigating them through complex regulatory

hurdles in an efficient manner. A key positive feature of PRIME includes the early appointment of a Rapporteur, working with the company, helping to clarify what types of questions the regulators would expect to be addressed during development, not only leading to an (initial) approval, but long-term, post-initial approval. This has now evolved to the current two-entry point PRIME scheme; the first being early for small and medium-sized enterprises (SMEs)/ academia-only; the other (main) entry point later in the development lifecycle (proof-of-concept phase), open to all companies. This second entry point is analogous to the FDA’s breakthrough therapy designation (BTD) entry point – the US regulatory fast-track process. The EMA gave PRIME the structure and legal hook, building into the accelerated assessment (AA) process.

An integrated approach

With increasing involvement of multiple stakeholders (regulators, HTA bodies / payers, manufacturers, patient groups), an integrated approach is needed to determine go/no-go decision on whether to pursue early access for an asset, the most appropriate early access pathway, a flexible clinical development strategy, and evidence generation plan.

In 2010, EMA initiated a pilot project on parallel scientific advice with HTA bodies that allowed companies to receive simultaneous feedback from both the EU regulators and HTA bodies on their development plans for medicines. This joint platform for parallel consultation (i.e. that the drug development, pre- and post-licencing, providing advice to developers. This parallel advice is also a feature of PRIME, but it is available to all medicines under development. Parallel advice with different HTA bodies (some markets with multi-HTA bodies) is still currently challenging (especially in terms of resource). Although, EMA and the European Network for Health Technology Assessment (EUnetHTA) are now stepping up their efforts to provide developers with simultaneous, coordinated advice on their development plans to facilitate alignment of data requirements. These regulatory-HTA body interactions should address areas of development which are less harmonized, such as optimization of trial data sources, so the same studies provide answers to several stakeholders. Also, contextualize the potential benefits and value the new medicine will create, as compared

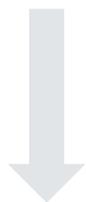
to existing treatments in an early value proposition strategy. For example, there needs to be further general discussions between regulators and HTA bodies on how to best generate and assess quality of life (QoL) and patient reported outcomes (PRO) data.

A medicine’s eligibility for an early access program is based on its intention to treat a serious condition, a promise of significant improvements in clinical benefit and patient-relevant outcome(s) over existing treatment. In early development, the evidence of potential to address unmet medical need may be demonstrated in nonclinical models, mechanistic rationale, or pharmacologic data. Later, preliminary clinical data should indicate the drug’s potential. Many products fulfilling the criteria for orphan designation may also qualify for early access. Therefore, the feasibility of orphan drug designation should be evaluated as part of any early access strategy, and vice versa. Coordinated early access and orphan designation strategies are particularly crucial if a medicine has the potential for significant benefit in both rare and non-rare conditions or multiple orphan subsets.

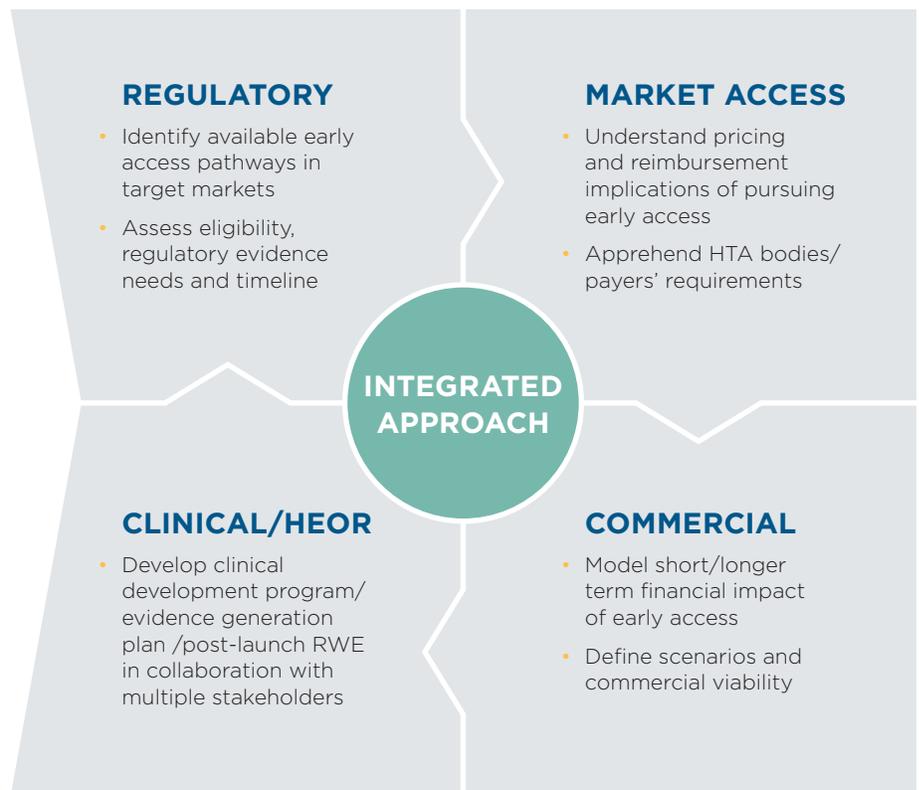
**MAKE A GO/NO-GO
DECISION ON
EARLY ACCESS**



**DEVELOP AN EARLY
ACCESS PLAN
(INCL. EVIDENCE
GENERATION)**



**CONSIDER
DOWNSTREAM
IMPLICATIONS**



In many therapeutic areas (excepting rare diseases or for medicines treating small populations where the collection of data by traditional routes is difficult), information from RCTs is almost exclusively the basis for regulatory decisions. Adaptive, novel and non-conventional pathways utilizing RWE to shorten and accelerate development should be considered in an early access strategy, particularly for orphan drugs. This strategy will be discussed with during the parallel scientific advice, ideally agreeing on one set of studies that will address the requirements of both regulators and HTAs.

To gain early access, the entire toolbox of knowledge generation is used to underpin regulatory and coverage decisions, including conventional RCTs, real-world (pragmatic) RCTs, and all variations of (non-randomized) observational studies.

The rising influence of patients, patient representatives and their active participation in decision-making emphasizes patient preferences, which are increasingly relevant in both benefit/risk and value judgements. Patient-centred evidence (including Patient-reported outcomes (PROs)) is therefore a cornerstone of early access, and should be integrated and pre-planned early on in a life-cycle approach throughout the development process, including post-authorization.

Conclusions

Obtaining a marketing authorization is the primary goal of sponsors. Considerations of (payer) access follow, along with all decision makers (including healthcare professionals and patients). An early access strategy will consider the requirements of all stakeholders from the beginning of the development lifecycle and, where possible, are aligned to optimize drug development. There will be an, inevitable, access versus evidence trade-off, but consultation with all the stakeholders during development will help identify potential benefits and risks relevant to those stakeholders. In rare diseases, early access strategies, benefit/risk and value demonstrations are often uncharted terrain, requiring highly specific expertise and experience.



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