

EARLY ACCESS TO MEDICINES FOR UNMET NEEDS

A BRIEF REVIEW OF REGULATION IN SELECTED MARKETS

By Richard Huckle

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. Early access pathways are evolving, with the aim to facilitate and accelerate development, marketing authorisation and access of medicines to patients in areas of high unmet needs.

We are becoming increasingly familiar with US FDA fast-track status and breakthrough designation, together with accelerated and conditional EU approval. Here we explore regulatory systems supporting early access in selected markets outside the US and EU. In addition to the assessment of regulatory pathways, we will examine the role of expanded access or compassionate use schemes/named patient programmes to support access along with specific local data requirements.

US and EU As Baseline

Early access pathways for biomedical product marketing approval have attracted substantial attention, as Sarepta Therapeutics' drug Exondys (eteplirsen) gained accelerated approval based on clinical data from just 12 patients. "Breakthrough" and "Fast-Track" are frequently heard buzzwords in the pharmaceutical arena. Looking at development times of up to 17 years from early R&D to product approval with further two years for pricing and reimbursement, it appears that the biopharmaceutical industry is rather "Slow-Track". Despite significant advances in medical science, there are still numerous patients without appropriate treatment options.

In the US, four "expedited" or "conditional" pathways for novel products for serious diseases or unmet medical need are available: Fast Track designation (FT), Breakthrough Therapy designation (BTD), Priority Review designation (PR), and Accelerated Approval pathway (AA). Characteristics and distinguishing elements of these pathways have been well described by the FDA in a 2014 "Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics". Proposed benefits include increased levels of communication and commitment between the FDA and product sponsors, greater roles for surrogate endpoints, transfer of burden of evidence generation from pre- to post-authorisation phases, and shortened review timelines. In 2012, the FDA launched BTD to facilitate and expedite the development and review of new drugs for serious or life-threatening

conditions. Following the FDA's designation of a product in a defined indication as breakthrough, the developer benefits from:

1. Frequent meetings with the FDA
2. Intensive guidance on efficient drug development
3. Organisational commitment of senior managers
4. Opportunity for rolling review
5. Priority review

Similar (but different) schemes exist in Europe. The European Medicines Agency (EMA), instituted Conditional Marketing Authorisation (CMA) procedures in 2006 for products where:

1. Benefit/risk balance is positive
2. It is likely that comprehensive clinical data will be provided
3. Unmet medical needs will be fulfilled
4. Benefit to public health of immediate availability outweighs risks that additional data are still required.

These EMA-CMA approvals require annual renewal and can be converted to full marketing authorisations upon review of definitive data generated during the conditional approval period.

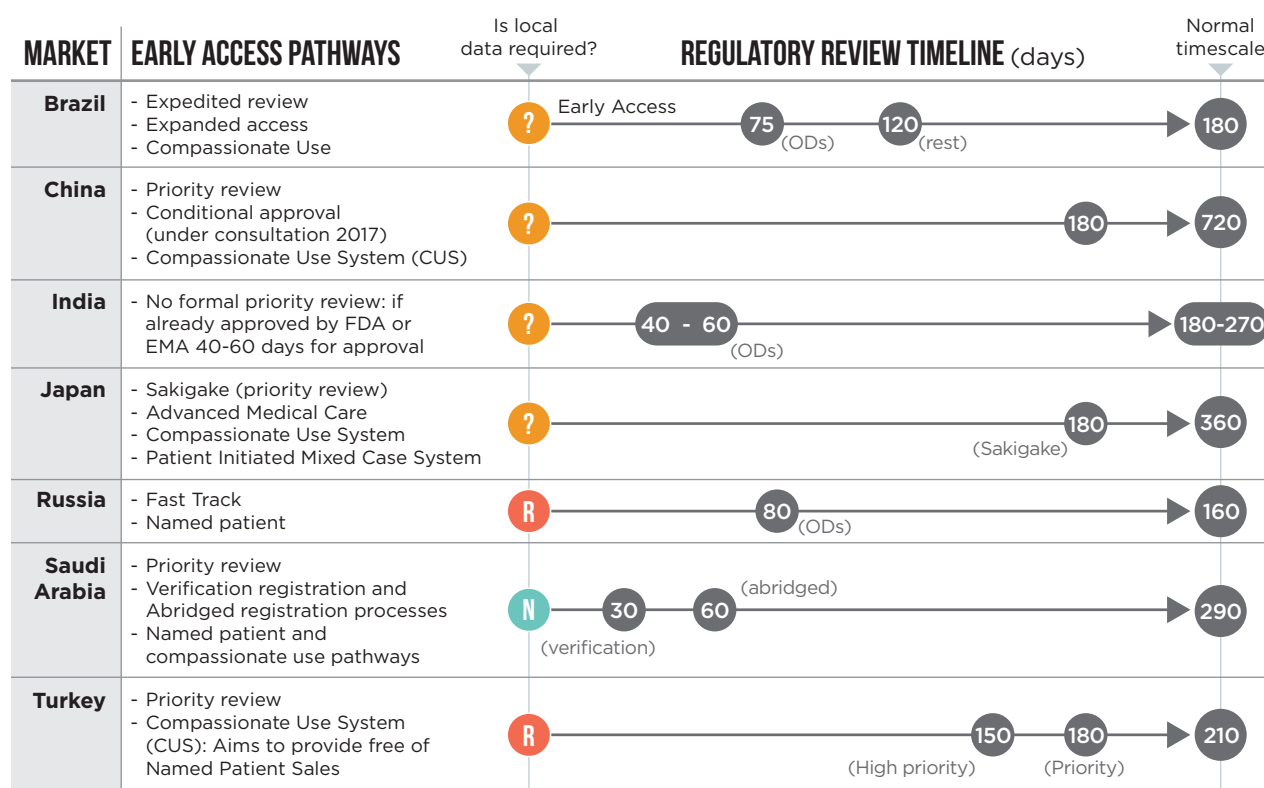
Partially in response to the FDA BTB, EMA responded in 2016 by implementing its own breakthrough concept, named PRIME. PRIME stands for PRiority MEdicines and is intended to support the development of medicines addressing unmet medical needs. Sponsors of PRIME designated products benefit from early and enhanced dialogue with regulators at EU-level and accelerated assessment of marketing authorisation applications.

Regulatory Partnerships

Regulations are becoming more global. Bilateral agreements and collaboration between the regulators of different markets are increasingly becoming a common occurrence (e.g. FDA and EMA, FDA and CONEP (Brazil), MHRA (UK) and CDSCO (India)). If one regulator inspects a company, manufacturing facility or clinical trial site, that information will be able to be shared with other regulators. Another trend towards a holistic approach can be seen in the synergies between regulations and subsequent harmonisation of regulation, guidelines and requirements (e.g. IDMP regulation, ICH guidelines and alignment of the CDISC Global Clinical Trial Registry with the IDMP regulatory compliance). This alignment will bring data integrity from R&D through to the supply chain, further highlighting the importance of data reusability.

Other Selected Markets

Since many countries in South America, Africa and Asia grant preferential review to drugs approved by regulators in the US and the EU, expedited approval in these regions potentially translates into world-wide approval of a given drug. With multinational adoption of most expedited approval pathways, it may be tempting for sponsors to simultaneously apply for designations in all regions. However, if any one regulatory agency disagrees with the designation request, it is likely that other regulators will follow suit as well. So, the best strategy is to get successful designation in one region and then try to use that in others. See Figure 1 for examples of markets with (or without) early access pathways (both regulatory approval and EAP or CUS).

Figure 1. Is early access/approval available in other markets? Do we need to generate local data?

R Required **?** Maybe (ICH E5) **N** Not mandated

Early Access Programmes

Governments worldwide have created provisions for granting access to drugs prior to approval for patients who have exhausted all alternative treatment options and do not match clinical trial entry criteria, these are so called Early Access Programmes (EAPs) or labelled Compassionate Use Schemes (CUSs). Some markets regulation allows patients to access drugs that are approved outside of the region, but not yet in their home countries. EAPs are governed by guidelines and legislation that vary by country, defining access criteria, data collection, supply and control of the drug distribution. Some countries (e.g. Canada and Australia) have well defined EAP, Special Access Programme (SAP) and Special Access Scheme (SAS), respectively. EAPs can be put in place at any stage of development post-phase II and can run in parallel with phase III clinical trials, until

market authorisation is granted. Reporting data about efficacy, safety and occurrence of adverse events to the responsible health authority are usually mandatory requirements. Mostly it is the treating physician that is responsible for initiating the request, monitor and report any output coming for the utilisation of the unauthorised drug (in clinical trials, it is the sponsors responsibility). Regulations differ widely among countries, due to differences in national medical practices, resources available, product funding, hospital structures and national insurance systems.

While patients, hospitals and/or national insurance systems bear the costs in some countries, the sponsor is expected to provide Compassionate Use products free of charge. An important consideration is that if a drug is charged for, then the obtained price may be used as future benchmark for pricing and reimbursement committees.

Conclusions

Advances have been made in fast tracking medicines to patients with unmet needs. We have described some evolution by the regulators to create accelerated routes and health authorities allowing patients access to experimental or unapproved medicines. The developer needs to carefully evaluate (risk:benefit) these options before embarking on any of these routes, as whilst providing (mainly) advantages to patients where certain limitations could apply.

Likewise, the decision to implement an EAP should be carefully considered and a sponsor should ask important questions such as when to offer access and for which patients, as there might also be many drawbacks tied to its implementation. Existing regulations do not force companies to offer access to drugs prior to approval or launch.

In addition to providing significant benefit to patients with unmet needs, EAPs can offer important benefits in terms of increased and earlier access to the sponsoring manufacturer. EAPs can be a part of a global market access strategy, generating development strategies that are increasingly innovative and global in scope. Huron can help you develop your regulatory and market access strategies.



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