HURON

THE NEED FOR SPEED...

enhancing access to treatments for unmet needs

By Richard Huckle

The high and ever-increasing global unmet need for patient access to medicines, together with the growing complexity involved with drug development, requires a coordinated stakeholder approach to tackle these challenges. For patients, considerable barriers still exist in terms of access to appropriate diagnosis, care and limited or non-existing treatment options. Governments and policymakers are responding to these with early-access pathways, which aim to facilitate and accelerate drug development, marketing authorisation and ultimately, 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 assessment and conditional marketing authorisation (CMA) in the EU. Here we explore some emerging markets for ways their regulatory systems are approaching this problem and supporting early-access. In addition to the assessment of regulatory pathways, we will examine the role of compassionate use schemes (CUS)/named patient programs (NPP) to support affordable access to currently unapproved medicines.

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US, Japan and EU as Benchmarks?

"Early-access pathways" for medical product marketing approval have attracted substantial attention and make high profile media headline news such as Sarepta Therapeutics' drug Exondys® (eteplirsen) gaining accelerated approval based on clinical biomarker data from a small group of Duchenne Muscular Dystrophy patients [1]. "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 negotiations, it appears that the biopharmaceutical industry is somewhat "Slow-Track". Despite significant advances in therapeutics, there are still too many patients without appropriate treatment options.

In the US, four "expedited" or "conditional" pathways for novel products addressing 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 FDA in a 2014 paper "Guidance

1. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm521263.htm

for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics". Proposed benefits include increased levels of communication and commitment between 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 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 BTD (and Japan's Sakigake 'Forerunner'), EMA responded in 2016 by implementing its own breakthrough concept, named PRIME (PRIority Medicines) which 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. Identification of Medicinal Products (IDMP) regulation, International Council for Harmonisation (ICH) guidelines and alignment of the Clinical Data Interchange Standards Consortium (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. In the accelerated approval pathway, Sakigake, in Japan, an applicant should place greater importance on the development of its product from an early stage in Japan and plan to submit a Japanese new drug application (JNDA) prior to other countries (although simultaneous submission is acceptable). In addition, it is desirable that either or both first-in-human (FIH) and/or proof-of-concept

(POC) studies are conducted in Japan in order to confirm development is progressing in Japan. The best (lower risk) strategy is to obtain a successful designation in one region (ideally a market which is part of the International Conference on Harmonisation (ICH)) and then expand to other markets. See Figure 1 for examples of markets with (or without) early access pathways.

Reliance pathways to Facilitate Regulatory decisions

Broadly speaking, regulatory review/approval pathways available include Recognition, Verification and Abridged review procedures:

Recognition review is a model in which national competent authorities (NCAs) review medicinal products intended to be marketed in other countries or regions other than their own. Examples of such review procedures are EMA's Mutual Recognition Procedure (MRP), Swissmedic's Marketing Authorisation for Global Health products and medicines reviewed through the WHO collaborative prequalification program). With such review procedures, the authority of the country/region where the product is intended to be marketed/used can directly recognise the outcome of this review.

Verification procedures are used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more NCA(s) (usually coming from an ICH member country). The main responsibility of the importing NCA is to 'verify' that the product intended for local registration has been duly registered by the exporting NCA as declared in the application and that the product characteristics (use, dosage, precautions) for local registration conform to that agreed in the reference authorisation(s). Additionally, there needs to be the assurance that the product is equal or similar to that approved by the reference agency.

The **Abridged** review model relies on assessments of scientific supporting data that has been reviewed and accepted by NCAs but includes an 'abridged' independent review of a certain part of the registration dossier of the product (e.g. relevant to use under local condition). This might include a review of the pharmaceutical quality (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/ culture and patterns of disease and nutrition.

Expedited Regulatory Pathways for medicines targeting unmet medical need:

1. Expedited review

Regulatory authorities expedite the review of certain products to enable faster approval. The expedited review time is substantially shorter than the standard review period. A decision on which a product to grant expedited review is normally based on its importance to public health aspects and unmet need defined within that market. Some markets have lists of preferentially required medicines (not necessarily medicines that meet unmet need requirements or orphan drug designation in other markets) and qualifying products from this list can be subjected to an expedited review process.

2. Expedited submission

'Expedited submissions' are being referred to as 'rolling submissions' and information and data-packages can be submitted and reviewed as they become available even before the official submission date. There is, for example, no need to wait for the availability of the full clinical data before submission of the earlier available, pre-clinical data. This allows NCAs to review available data sets as soon as they are available and may allow the expediting of regulatory procedure and may also disclose any future development bottlenecks and plan for post-approval study requirements.

3. Expedited development

Expedited development approaches allow for earlier submission and approval with a data set which may be less complete than that from a standard development programme. This approach is exclusively reserved for products which address a high unmet medical need in a serious or debilitating condition and where the data are nonetheless adequate to demonstrate a positive benefit-risk profile. The most common

example of expedited development is approval based on convincing Phase 2 clinical data and/or data based on well validated surrogate endpoints. Such approvals (e.g. EMA Conditional Marketing Authorisation, FDA Accelerated Approval pathway) are often only granted on the basis that the benefit-risk profile observed during clinical studies will be maintained post-approval with certain conditions. The success of such approaches depends on the ability of the regulatory agency to apply the principle of 'regulatory flexibility' in defining the regulatory requirements for an application. This can entail reduced data requirements, where justified, based on medical need, but can also rely on evolving scientific developments or new and innovative approaches to drug development (e.g. adaptive clinical trial designs, modelling and simulation, extrapolation).

Centre for Innovation in Regulatory (CIRS) R&D Briefing 67 (2018) examines the performance of six major authorities approving new drug by such facilitated pathways in 2008 -2017.

	MUTUAL RECOGNITION (EG. ABRIDGED, VERIFICATION REVIEW)	**FACILITATED REGULATORY PATHWAY** (EXPEDIATED DEVELOPMENT)
Argentina	✔	
Australia	✔	✔
China		✔
Egypt	✔	
Indonesia	✔	
Israel	✔	
Mexico	✔	
Singapore	✔	
Souith Korea	✔	✔
Taiwan	✔	✔
Ukraine	✔	

Figure 1 - Expedited pathways currently in place in selected markets (including Liberti et al, 2016)

Early access programmes

Thus far, we have looked at review/approval pathways. However, as mentioned, the development and review processes to approve medicines for market takes a considerable amount of time and effort. 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). Each EAP varies from individual, named patient (NPP) to needs-based cohort programmes such as Compassionate Use Schemes (CUSs). Other terms associated with EAPs include Managed Access Programs (MAPs), Expanded Access, Treatment IND, Special Access or Temporary Use. Some countries (e.g. Canada and Australia) have well defined EAP, Special Access Programme (SAP) and Special Access Scheme (SAS), respectively. 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. EAPs can be put in place at any stage of development (usually) post-phase II (there are notable exceptions) and can run in parallel with phase III clinical trials, until market authorisation is granted, and patients have access to approved medicines. Reporting data about efficacy, safety and occurrence of adverse events to the responsible health authority are usually mandatory requirements (some markets do not allow the collection of any data (except adverse events) obtained from an EAP since they may not be classified as a study or research).

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 sponsor responsibility). Regulations differ widely among countries, due to differences in national medical practices, resources available, product funding, hospital structures and national insurance systems etc.

IMP in active clinical development	• Does not threaten enrollment or conduct of controlled clinical trials
Meeting regulatory requirements	• Regulatory requirements not clearly defined nor harmonised (as with clinical trials) • In many cases ethics committee/IRB approval is required
Cost of an EAP	• Complexity of design and conduct • Study sites executing the program in a GCP-compliant manner • Plans, processes and the management of the EAP must be nimble and dynamic
Adequate supply of IMP	• To perform necessary clinical studies as well as to provide EAP • Sufficient and adequate stability data, etc. • Labelling and important requirements
Financial sustainability and a strategy for post-authorisation	• Patients supported until treatment is commercially available – how long? • Reimbursement/sales (where permitted) may cover some costs
Benefit-risk profile	• "Do no harm" • Continuous benefit-risk communication of any changes to the profile • Pharmacovigilance

Figure 2 - Overarching principles/requirements of EAPs (Jarrow et al, 2016)

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. Some health authorities also cap the price which can be reimbursed under an EAP (e.g. France's TUA).

A notable exception (in many respects), is the US Right-to-try (RTT) Bill. RTT is intended to give people with fatal illnesses a way to access drugs that are still experimental (not necessarily in clinical stages) and not approved for use. There has been much scrutiny (and controversy) associated with RTT. Dr. Scott Gottlieb, the commissioner of the FDA has expressed concerns, partly due to there not being an FDA review requirement (there is for other US expanded use schemes, such as Treatment or Emergency IND to facilitate access which does receive a health authority review and endorsement) and liability for any failures associated with the experimental treatment (such as adverse events or even death) rests on the patient, not the manufacturer, treating physician or health authority. He argues that such failures could delay or stop the development, review/approval process and prevent other patients benefiting from the experiment treatment.

> Early access pathways are a dynamic area of regulatory science.

REQUIREMENT	TYPICAL EAP	RTT
NCA/FDA approval	✔	✘
IRB/EC approval	✔ / ✘	✘
HCP approval	✔	✔
Manufacturer approval	✔	✔
Informed consent	✔	✔
Safety reporting	✔	✔ ?
Liability	Manufacturer	Patient

Figure 3 - Comparison of typical EAP requirements compared with Right-to-try (RTT) (Wendler et al, 2017)

Conclusions

Early access pathways are a dynamic area of regulatory science. Advances have been made in advancing medicines to patients with unmet needs. Some evolution (even revolution) by the regulators to create accelerated routes and health authorities allowing patients access to experimental or unapproved medicines have been described. The developer needs to carefully evaluate these options (benefit:risk) before embarking on any of these routes, as whilst providing (mainly) advantages to patients there certain limitations could apply.

Likewise, the decision to implement an EAP should be carefully considered and a sponsor/

manufacturer 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.

References

1. Centre for Innovation in Regulatory Science (CIRS). The impact of the evolving regulatory environment on the approval of new medicines across six major authorities 2006-2015, R&D Briefing 59 (2016) Available from: http://www.cirsci.org/wp-content/uploads/2016/05/cirs_rd_-briefing_59_23052016.pdf
2. Centre for Innovation in Regulatory (CIRS). New drug approvals in six major authorities 2008 -2017: Focus on the availability of medicines and company size R&D Briefing 67 (2018) Available from: http://www.cirsci.org/wp-content/uploads/2018/05/CIRS-RD-Briefing-67-04052018_FINAL.pdf
3. EMA. Guideline on compassionate use of medicinal products, pursuant to Article 83 of Regulation (EC) No 726/2004 (2007).
4. Gottlieb S. Examining Patient Access to Investigational Drugs FDA [Internet] (October 3, 2017) Available from: https://www.fda.gov/newsevents/testimony/ucm578634.htm
5. Jarow JP, Lemery S, et al. Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period. Ther Innov Regul Sci. (2016) 50(6): 705–709.
6. Liberti L, Breckenridge A, Hoekman J, Leufkens H, Lumpkin M, McAuslane N. Accelerating access to new medicines: current status of facilitated regulatory pathways used by emerging regulatory authorities. J Public Health Pol (2016) 37(3): 315-333.
7. Patil S. Early access programs: Benefits, challenges, and key considerations for successful implementation. Perspect Clin Res. (2016) 7(1): 4–8.
8. Wendler T, Mongiello F, McLinn J, and Bellina M. Right to Try Act of 2017: Senate Bill 204; 115th Cong. § 2(a) (2017)
9. UK Government Office for Life Sciences. Guidance Early access to medicines scheme (EAMS): task group and principles [Internet] (Published 10 May 2016) Available from: https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works/early-access-to-medicines-scheme-eams-task-group-and-principles
10. US FDA. Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics (2014)
11. US FDA. Expanded Access to Investigational Drugs for Treatment Use —Questions and Answers Guidance for Industry [Internet] (updated October 2017) Available from: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation /guidances/ucm351261.pdf
12. US FDA. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review [Internet] (updated February 23, 2018) Available from: https://www.fda.gov/forpatients/approvals/fast/default.htm
13. US FDA. News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy [Internet] (September 19, 2016) Available from: https://www.fda.gov/newsevents/testimony/ucm578634.htm

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