Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

March 2020 (Volume 34, Issue 3)

PEER REVIEWED

Expediting Drug Development Regulatory Pathways Globally

Aman Khera

Medicine and healthcare are evolving at an impressive rate. Artificial intelligence models, for example, are beginning to aid the detection of cancer and other serious diseases. The onset of digital therapeutics is creating innovative avenues for improved interventions. To keep pace with such transformation, drug development must follow suit.

Data and technology advances are fueling the current speed of innovation and are expanding the breadth of the drug discovery pipeline to an extent where we can no longer navigate the drug development process fast enough. Already, the industry is struggling with too many trials and too few patients. If we continue with these existing drug development models, we will experience even slower patient recruitment and longer trials—a stark contrast to recent efforts aimed at shortening development pathways.

For example, new guidance released in November 2019 by the U.S. Food and Drug Administration (FDA) shows support for the use of adaptive clinical trial designs.{1} At the same time, the final concept paper for the third revision of the ICH E6(R3) Guideline for Good Clinical Practice from the International Council for Harmonization (ICH) was endorsed by the organization's Management Committee.{2}

The evolution of such guidance and endorsements demonstrates increasing industry flexibility for accommodating technology and data sources in clinical trials. We must continue to embrace the power of digital technologies and their potential to transform how clinical trials are conceived and realized.

Likewise, expedited pathways for drug development have significantly increased in the past several years. Global regulatory agencies are making more accommodations for studies involving pediatric populations, rare diseases, and other indications challenged by limited patient populations and other data-gathering obstacles. Rather than their historical reputation as "the 'no' people," regulatory agencies today are taking a more empathetic and collaborative approach to get beneficial therapies to market—and to patients—sooner. When properly allied, these agencies can become supportive resources for sponsors and researchers.

Efficiency and Time Savings

Adhering to the adage "time is money," anything sponsor companies can do to shorten an effective drug's time to market is valuable. Expedited pathways can provide an opportunity for shorter clinical development, meaning that drugs can potentially reach markets and patients faster. Therefore, sponsor companies should seriously consider not only the drug development journey, but also how to optimize it through the use of one or more expedited pathways.

Not every drug will qualify for an expedited pathway, of course. Currently, the common theme among most of these regulatory pathways involves the potential for a drug to meet unmet clinical needs and/or work better than existing therapies. Still, there are many avenues for using expedited pathways available in the United States (U.S.), European Union (EU), Japan, and China.

Expedited Pathways in the U.S.

In the U.S., early engagement with the FDA is strongly encouraged when applying for any expedited pathway designation. Sponsors that do so typically benefit from the fact that regulatory scientists essentially become integral members of the development team, helping guide sponsors along the development path.

Expedited pathways in the U.S. include:

- **Breakthrough therapy designation**. This designation debuted in 2012 and occurs early in the drug development journey. The FDA notes, "*Breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. A breakthrough therapy designation conveys all of the fast track program features…, more intensive FDA guidance on an efficient drug development program, an organizational commitment involving senior managers, and eligibility for rolling review and priority review*."{3}
- **Fast track designation**. Fast track designation typically transpires during the Investigational New Drug phase of drug development.{4} It *"…emphasizes the critical nature of close early communication between the FDA and sponsor to improve the efficiency of product development*."{5} The FDA adds, "*Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need… If there are available therapies, a fast track drug must show some advantage over available therapy…*"{6}
- **Accelerated approval**. The Accelerated Approval Program typically is used a little later in the drug development journey. It allows the use of a surrogate endpoint to speed FDA approval, although Phase IV confirmatory trials still are necessary. "*The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that treat serious conditions, and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image,*

physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit."{7}

- **Priority review**. Among expedited pathways in the U.S., priority review arises latest in the drug development process. Although priority review does not affect the length of the clinical trial period, it shortens the application review period from the standard 10 months to six months.{8}

Expedited Pathways in the EU

Expedited pathways available in Europe tend to occur toward the end of the drug development journey. Nevertheless, just as with the FDA in the U.S., sponsors are encouraged to engage and collaborate with the European Medicines Agency (EMA) and other regulatory agencies early in the development process. This might take the form of receiving scientific advice from the EMA, for instance, or national scientific advice from individual agencies.

Meanwhile, in the post-Brexit case of the United Kingdom (UK), there still will be access to a National Scientific Advice procedure with the Medicines and Healthcare products Regulatory Agency (MHRA), but the precise mechanics of expedited pathways in the UK are currently unknown.

Expedited pathways in Europe include:

- **Accelerated assessment**. The review of a drug marketing authorization application by the EMA typically happens within 210 days. Accelerated assessment enables approval within 150 days for products *"…expected to be of major public health interest, particularly from the point of view of therapeutic innovation*."{9}
- **Authorization under exceptional circumstances**. When a dearth of data exists and cannot be obtained—particularly in rare disease studies involving exceptionally small patient populations—this pathway allows for ongoing safety monitoring after a drug is on the market with annual risk/benefit reassessments.{10}
- **Adaptive pathways/licensing**. This designation often is used when more data are needed to widen a drug's indications. It originally was termed "adaptive licensing," but has since been renamed "adaptive pathways."{11} The focus is on early dialogue between

sponsors and regulatory agencies, as well as an iterative development approach that leverages real-world data.

- **Conditional marketing authorization**. The conditional marketing designation offers temporary, one-year approval in situations where the benefit of immediate drug availability outweighs the risk of less comprehensive data than normal.{12} Unlike "authorization under exceptional circumstances"—which grants approval when data are not obtainable—conditional marketing authorization is allowed when it is likely that comprehensive data eventually will be gathered.
- **PRIME** (**Pri**ority **Me**dicines). The PRIME scheme, which was launched in March 2016, is quite advantageous for sponsors in early clinical development stages. It provides early and enhanced scientific and regulatory support, allowing for multiple scientific advice meetings with EMA, in addition to the possibility of parallel advice with EMA and Health Technology Assessment bodies.{13} It is aimed at optimizing clinical trial design as well as engaging technology and payer perspectives.

Expedited Pathways in Japan and China

Even with the best clinical trial strategies in place, there are multiple challenges that may require sponsor companies to look outside the conventional U.S. and EU regions. Regardless of whether the sponsor needs to expand its patient recruitment area or wants to quickly bring a product to market in new areas, it is critical to understand the regulatory environments around the world. For instance, Japan and China could deliver worthwhile patient recruitment options.

Japan

Japan's regulatory landscape aligns somewhat with the EMA and the FDA. Many of the expedited pathways offered by Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and its Ministry of Health, Labor, and Welfare (MHLW) apply toward the end of the drug development journey. They include:

- **Priority review**. This pathway allows a shortened review period—nine months vs. 12 months—for all orphan drugs, as well as for any drugs that may deliver better outcomes for serious indications.{14} This also applies to products for treating a serious disease

when no standard therapy exists or if there is superior clinical usefulness compared to existing products in terms of quality of life of patients, efficacy, or safety. (Although orphan designations are not an expedited pathway in the EU or U.S., it is common for orphan drugs in those regions to also utilize expedited pathways.)

- **Conditional early approval system**. This designation speeds the approval process for drugs that may offer better outcomes for serious indications, but for which confirmatory clinical trials are difficult because of small patient populations. The post-market surveillance period is lengthened.{15} Instituted in October 2017 in Japan, the conditional approval system may be granted if a drug is intended to treat a serious condition or if there is no standard therapy that exists. This system may also be used if superior clinical usefulness can be demonstrated compared to existing products in terms of quality of life of the patient, efficacy, or safety, and it is problematic or would take too long to conduct a confirmation study.
- **Sakigake designation system**. Available since 2015, the Sakigake designation encourages early engagement with authorities and aims to shorten the review period for innovative medical products first developed in Japan that satisfy certain criteria. To obtain this designation, products must show early promise of prominent effectiveness. The target review period for the designated products can be reduced to as short as six months, which is half the typical 12-month review period for pharmaceuticals. Benefits of the designation include *"...prioritized consultation (reduced waiting time), substantial pre-application consultation, expedited review (a target total review time of six months only for drugs, devices, and IVDs), the assignment of a PMDA concierge, and an extended reexamination period...*"{14,16}

China

There is less alignment between China's regulatory environment and the EMA and FDA. However, in 2017, China joined the ICH as a full regulatory member.{17}

China's focus for joining the ICH centered on resetting its regulatory processes for the approval of innovative therapies. Whereas it used to take roughly two years to obtain approval to conduct a clinical trial in China, it now takes 60 working days to gain approval from the National

Medical Products Administration (NMPA). Moreover, U.S. regulators now accept Chinese data. Additionally, a joint EU and China effort established in 2010 aims to promote information exchange and understanding of pharmaceuticals and other medical and regulatory science issues, and discussions are ongoing.{18}

A New Era of Collaboration

In the global effort to speed therapies to market, regulatory agencies are engaging with sponsors and with each other more than ever before. This collaborative spirit benefits not only the agencies, but also patients and sponsors.

For example, sponsors can now make parallel applications to the FDA and EMA for orphan drug designation via a single common form. Although the definition of rare disease and the requirements for orphan designation vary across regions, a sponsor company could submit for orphan designation to both agencies at the same time using the same data.

More recently, in September 2019, the regulatory agencies of Australia, Canada, and the U.S. announced that they jointly approved a combination immunotherapy for a form of endometrial cancer. This joint approval arose from an initiative called Project Orbis, which was set up by the FDA to enable agencies to collaborate on additional oncology treatment targets for previously approved therapies. Accelerated approval, priority review, and breakthrough therapy designations all were granted as the FDA conducted its review under the Oncology Center of Excellence's Real-Time Oncology Review pilot program.{19}

As far back as 15 years ago, the FDA Office of Hematology and Oncology Products began holding regular meetings with global regulatory agencies from Australia, Canada, Europe, Japan, Switzerland, and China. The FDA also has indicated that it is looking to collaborate further with global partners, reinforcing its commitment to serve the U.S. population and other global patient populations.

Likewise, agencies in some emerging markets now are open to other regions' approvals, acknowledging the detailed review process that products are subjected to in places such as the U.S. and Europe.

Strategic Teamwork for Better Outcomes

Pursuing expedited pathways in multiple geographic regions (e.g., U.S., EU, Japan, and China) may give sponsor companies several advantages. Tapping into global populations not only serves to increase patient recruitment, but also may help ensure more accurate clinical knowledge of how a product works within diverse patient populations.

However, sponsors cannot afford to think of regions in a staggered manner if they wish to develop products that truly benefit patients globally. They must recognize the similarities and differences among regions from both the development perspective and the payer perspective. In addition, they must understand the vital role that regulatory expertise plays in adherence to an optimal path.

In the rapidly changing global regulatory landscape, strategic planning is essential. A sound starting point is to consider a regulatory strategy plan coupled with a clinical development plan, which will assist in awareness of the necessary timing and requirements for expedited pathways. Plans should be flexible and adaptable according to data, intelligence, and results.

A good regulatory partner will have the expertise to know when and where to employ various expedited pathways and to help sponsors decide an optimal strategy. They will also have experience effectively managing relationships with regulatory agencies—from presenting applications in a timely and effective manner, to preemptively answering regulators' questions and addressing their concerns. Well-thought-out, high-quality submission documents are crucial whether a sponsor is requesting a meeting or applying for a designation.

Today, global clinical trials and expedited pathways give sponsors practical opportunities to drive faster, more efficient drug development. A primary key to success, however, is the early engagement of regulatory agencies. Although these agencies stand ready to assist, full engagement is not a theoretical exercise.

There are many intricate pieces to the puzzle of product development. Sponsors need to have dedicated, hands-on internal resources as well as experienced partners capable of staying on top of the quick decisions and frequent interactions. However, sponsors with the right pathway

strategies and resources in place can help ensure that promising drugs reach patients faster, providing hope for improved interventions and outcomes.

References

1. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. 2019. *Adaptive Designs for Clinical Trials of Drugs and Biologics, Guidance for Industry*. https://www.fda.gov/media/78495/download
2. International Council for Harmonisation. 2019. *Final Concept Paper ICH E6(R3): Guideline for Good Clinical Practice*. https://database.ich.org/sites/default/files/E6-R3_FinalConceptPaper_2019_1117.pdf
3. U.S. Food and Drug Administration. *FAQs: Breakthrough Therapies*. https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies
4. U.S. Food and Drug Administration. *Fast Track Designation Requests*. https://www.fda.gov/drugs/ind-activity/fast-track-designation-requests
5. U.S. Food and Drug Administration. *Fast Track Designation Request Performance*. https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/fast-track-designation-request-performance
6. U.S. Food and Drug Administration. *Fast Track*. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track
7. U.S. Food and Drug Administration. *Accelerated Approval Program*. https://www.fda.gov/drugs/information-healthcare-professionals-drugs/accelerated-approval-program
8. U.S. Food and Drug Administration. *Priority Review*. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review
9. European Medicines Agency, Human Regulatory. *Accelerated assessment*. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment
10. European Medicines Agency, Human Regulatory. *Pre-authorisation guidance; 1.10*. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance#1.-types-of-applications-and-applicants-section
11. Giuseppe N, Gianluca S, Annalucia S, Pasquale P. 2019. The Iterative Development of Medicines Through the European Medicine Agency's Adaptive Pathway Approach. *Frontiers in Medicine* 6:148. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6610487/
12. European Medicines Agency, Human Regulatory. *Conditional marketing authorisation*. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
13. European Medicines Agency, Human Regulatory. *PRIME: priority medicines*. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
14. Sumimasa N. 2019. Flexible and Expedited Regulatory Review Processes for Innovative Medicines and Regenerative Medical Products in the U.S., the EU, and Japan. *Int J Mol Sci* 20(15):3801. https://doi.org/10.3390/ijms20153801

15. Takao Y, Sandra B. 2018. PMDA Puts Regulatory Approval on a Fast Track. *DIA Global Forum*. https://globalforum.diaglobal.org/issue/may-2018/pmda-puts-regulatory-approval-on-a-fast-track/
16. Ministry of Health, Labour and Welfare. *Strategy of Sakigake as a Package*. https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-02.pdf
17. International Council for Harmonisation. *Members & Observers*. https://www.ich.org/page/members-observers
18. European Medicines Agency, Science Medicines, Health. *Dialogue with Chinese authorities on medicine regulation*. https://www.ema.europa.eu/en/news/dialogue-chinese-authorities-medicine-regulation
19. U.S. Food and Drug Administration. 2019. *FDA takes first action under new international collaboration with Australia and Canada designed to provide a framework for concurrent review of cancer therapies, approving treatment for patients with endometrial carcinoma*. https://www.fda.gov/news-events/press-announcements/fda-takes-first-action-under-new-international-collaboration-australia-and-canada-designed-provide

Aman Khera is Global Head of Regulatory Strategy at Worldwide Clinical Trials working out of Vancouver, British Columbia, Canada.