

## ARTICLE

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# ACCELERATED PATHWAYS: GLOBAL OPPORTUNITIES AND CHALLENGES FOR INNOVATORS

### NEW PATHWAYS, AND OPPORTUNITIES, EVERYWHERE

Accelerated Pathways (APs) for the development of new drugs in the U.S., Europe, and Japan – intended to bring needed and important new treatments to patients more quickly – have multiplied in recent years and have proven to present opportunities and benefits for patients and developers. But the varied nature and diversity of the accelerated pathways in these jurisdictions are generating new, unanticipated challenges that sponsors need to understand and plan for strategically.

In the U.S., APs include Fast Track (FT), Breakthrough Therapy Designation (BTD), Accelerated Approval (AA), and Priority Review (PR). And although the Orphan Drug pathway is not an AP *per se*, orphan drugs typically meet the qualifications for APs and are awarded some similar advantages (such as additional meetings with the FDA) due to their focus on unmet medical needs.

In Europe, APs include Accelerated Assessment (AA), Conditional Marketing Authorization (CMA), Authorization Under Exceptional Circumstances, and the Adaptive Licensing (AL) pilot. And in Japan there's the *Sakigake* (or "forerunner") fast-track development and review system, announced in 2014 and launched in 2015. It has designated six development drugs to date – five by Japanese sponsors, and one by a multinational sponsor (Merck's Keytruda

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[permbrolizumab] for unresectable, advanced, or recurrent gastric cancer).

In general, APs in all three regions offer the opportunity for shorter clinical development and/or review times, meaning that drugs can reach markets and patients faster, and developers can generate earlier revenue streams to invest in future research, as well as support necessary post-approval clinical and real world evidence (RWE) collection, while gaining (in many cases) first-to-market competitive advantages.

The similarities among the opportunities and benefits provided by APs in the U.S., Europe, and Japan, come along with important differences. That, combined with varied pre-approval data requirements for different AP pathways in different jurisdictions, and a growing number of involved stakeholders focusing on the risks and benefits of new products, is adding unanticipated complexity to an already tortuous road to market for new drugs. This makes it quite challenging for developers to take advantage of AP opportunities in all three regions. But developers must accept that challenge if they wish to appeal to a global audience for products that address indications and markets where early entry could help patients and establish market share.

This article will discuss what sponsors need to know to take advantage of APs in all three regions while minimizing risks and impediments to patient access. The key is understanding the opportunities and constraints presented by the various APs, and designing drug development strategies accordingly.

## La DIFFERENCE: THE U.S. AND EUROPE

Regulatory variability across jurisdictions – as well as the reimbursement differences between the U.S. and Europe – can dilute the benefits of winning an AP designation from a regulatory body.

Whereas in the U.S. the Centers for Medicare and Medicaid Services (CMS) must reimburse any drug approved by the FDA, private U.S. payers do not have to, and sometimes resist, although their ability to restrict access to new drugs is somewhat constrained by competition and public and political pressures. (In late January 2016, however, the Massachusetts Attorney General called for the lowering of the price of Hepatitis C drugs Sovaldi and Harvoni, both granted BTD designation, suggesting their price constituted an “unfair trade practice” under Massachusetts state law. Challenges from payer communities in the U.S. is new, and not previously foreseen in the context of APs. It may, indeed, foreshadow a potential change in the U.S. pricing

zeitgeist.) In any case, the influence of payers in the U.S. certainly does not compare to that of the regional Health Technology Assessment (HTA) organizations in Europe, which can deny reimbursement for any approved drug.

If European national HTAs (there are 28, and hundreds of subnational, regional HTAs, and they are all slightly different) decline to grant reimbursement for a new drug (or restrict its use beyond label), clearly the value of winning an AP designation is much diminished for its sponsor. Indeed, the fact that APs are often granted approval or marketing authorization with smaller data sets of clinical evidence can create hurdles for developers in gaining HTA approval for reimbursement.

For example, in 2013, the UK’s HTA, the National Institute for Health and Care Excellence (NICE), [declined to reimburse Novartis’ Afinitor](#), a treatment for advanced breast cancer, after it received accelerated FDA approval, and just days after it was approved by the European Medicines Agency (EMA), which is responsible for the monitoring of medicines for the European Union. NICE’s final guidance raised questions concerning “[uncertainties relating to how long it \[Afinitor\] could extend a person’s life,](#)” and whether it provided “[enough benefit to patients to justify its high cost](#)” – a reminder both of the influence of HTAs in Europe, and the variance in how regulatory bodies and HTAs view new products.

The clout of European HTAs such as NICE is partly why Europe’s Adaptive Pathway (formerly Adaptive Licensing) pilot, [launched by the EMA in March 2014](#), stresses the program as an opportunity “[to engage with HTA bodies and other stakeholders](#)” to accelerate patient access to needed new medicines.

Since the launch of the Adaptive Pathway pilot program, 59 products have been submitted as candidates. Twenty have been selected for in-depth discussions with the sponsor company (Stage 1). Of those 20, 11 were selected for Stage 2 meetings. The two main reasons given for the winnowing were that either the development of the product was too far advanced (that is, it was too late to change anything), or the required plan for the collection of RWE was deemed inadequate.

There are also important differences between the orphan drug (OD) designation frameworks in the U.S. and Europe. When a drug is designated as an orphan in both the U.S. and Europe, regulators will provide fee reductions (and free scientific advice for pediatric studies in Europe), 10 years of market exclusivity in Europe (seven in the U.S.), and waived payment of regulatory fees – all of which is a

boon, especially for smaller (less than 250 staff) U.S. developers. In the U.S., OD benefits include grants for development, additional meetings with the FDA, the waiver of the requirement for a pediatric plan, and waived fees for New Drug Applications (NDAs), and Biologic License Applications (BLAs). In the EU, the indication an orphan drug addresses must not only be rare, it must be debilitating, or life-threatening. In the U.S., the condition must be rare, and the reason for treatment must be explained – a somewhat more relaxed standard. The EMA also requires pre-clinical or clinical data to support the drug’s treatment, diagnosis, or prevention story, whereas the FDA requires only a rationale for the orphan status of the drug, not necessarily the supporting data.

Still, the similarities for orphan drug requirements in the U.S. and Europe are sufficient to make parallel applications for OD status in both jurisdictions feasible. Indeed, there is a form for applying simultaneously for OD status to the FDA and EMA.

For non-orphan drugs, submission becomes more complex with the larger patient populations addressed, and the granting of an AP designation, no matter the jurisdiction, does not guarantee ultimate approval. Indeed, the smaller data sets that are developed and provided for APs increase some of the risks inherent in all drug development.

In March 2013, for instance, the EMA’s Committee for Medicinal Products for Human Use (CHMP), issued a positive opinion for a CMA to Endocyte Europe’s Vynfinit (vintafolide), an orphan drug intended to be used for the treatment of ovarian cancer that has become resistant to platinum-based treatment. A CMA is much like the FDA’s Accelerated Approval, in which **“the benefits to public health of the drug’s immediate availability outweigh the risks inherent in the fact that additional data are still required.”** The Vynfinit application was based on one, 162-patient study, and the CHMP’s recommendation noted that it was granting the authorization even though **“comprehensive clinical data are not yet available.”**

However, before the authorization process could be completed by the European Commission, the company withdrew its application because the study it was conducting could not confirm benefit in ovarian cancer patients. In other words, the “additional data” could not support the accelerated application. The tradeoff between accelerated regulatory approval, and follow-on confirmation of efficacy and safety, can be a painful one.

Yet another challenge with the CMA designation is its requirement that a company return every year to renew its application. The EMA expects that a company’s drug will

gain full market authorization within a time frame defined at the time it issues the CMA, with the company providing more evidence – and patients – to justify it. This imposes a burden on developers seeking CMA that must be weighed strategically in terms of the developer’s resources and capabilities.

## WHEN IN JAPAN

The differences between the AP environment in Japan, compared to Europe and the U.S., also should be considered thoughtfully by drug developers.

In 2014, the Japanese Ministry of Health, Labor, and Welfare introduced the *Sakigake* (Forerunner) Review and Designation System, intended to facilitate **“rapid commercialization of pharmaceuticals, medical devices, and regenerative medicine products”** for “breakthrough therapies that addressed an unmet medical need” and “promise excellent efficacy on the basis of clinical trial data.” Similar to Priority Review, *Sakigake* designation allows for drugs to be approved after a six-month review, or “half the normal period,” and offers ongoing regulatory support and data review throughout development for the purpose of accelerating patient access to important new medicines. A significant benefit is that the government is willing to grant a 10%-to-20% price premium to *Sakigake* drugs that are approved for marketing.

Sponsors seeking *Sakigake* designation must abide by different rules than they do when they seek BTM in the U.S. Most importantly, they must apply for marketing approval in Japan first or at the same time (or within days) as they do anywhere else in the world. Japan will not consider any drug for *Sakigake* designation if an application has been filed previously elsewhere, or if the sponsor does not commit to filing in Japan first. The designation of Keytruda as *Sakigake* for the unresectable, advanced or recurrent gastric cancer indication (which is not approved in the U.S., where the indications of Keytruda are melanoma and metastatic non-small cell lung cancer) shows that *Sakigake* designation can be indication-specific.

The practical implication of the *Sakigake* program for sponsors is that global development planning and regulatory submission planning must take Japan’s first-to-file requirement into account. They must therefore design their development timelines well in advance if they intend to reap the benefits of the designation.

The Japanese government also passed a 2014 law establishing a conditional approval framework for regenerative therapies, which would be allowed to enter

the Japanese market with a minimum of clinical data, and would be subject to ongoing clinical studies and safety surveillance while on the market.

As in the U.S. and Europe, Orphan Drug (OD) status in Japan offers developers [a review timeline shortened by half](#), a variety of tax credits, and, as in the EU, 10-year market exclusivity.

To be considered for OD status in Japan, the patient population an OD addresses must be smaller than 50,000 patients in Japan. (In the U.S., the condition the drug treats must affect fewer than 200,000 people in the US, and in the EU the requirement for an OD is that it must apply to not more than five patients in 10,000 in the EU.)

Finally, as in Europe, the cost/benefit calculation is an important consideration in Japan, perhaps to a greater extent than in the U.S., although all three regions are showing growing concern about the larger economic impacts of the price of medicines. Japan's demographics (specifically its aging population and declining birth rate) are driving rising health care expenses in delivering universal coverage, and placing pressure on the national budget. The government's plan is to accelerate access to important innovations that improve the health of the population (while paying premium prices for it), as well as to promote a much deeper penetration of cheaper generic drugs that can help rebalance the health care budget.

## MEETING THE GLOBAL CHALLENGE: BALANCING OPPORTUNITIES AND CHALLENGES

To reap the benefits afforded by AP designations in the U.S., Europe, and Japan, sponsors must learn to balance their opportunities and challenges, navigating both in a way that meets the needs of all stakeholders: the sponsors themselves, regulators, payers, physicians, and patients.

To begin, it is critical to target the right indication with the right drug, understanding that the aim must be an unmet medical need. A condition with little morbidity, where effective treatment options are available, will likely not qualify for an AP anywhere in the world. Conversely, a drug for a late stage cancer, where few or no treatment options are available, most likely would.

For example, GSK's Arzerra (ofatumumab), a monoclonal antibody, [received accelerated FDA approval as a breakthrough therapy in 2013](#) to address previously untreated patients with chronic lymphocytic leukemia who could not have fludarabine-based therapy. After receiving the FDA BT, GSK applied to the EMA for a CMA designation (which it received) as a therapy for patients who cannot have fludarabine-based therapy. In March

2015, GSK swapped its oncology portfolio for Novartis' vaccine business in a \$16 billion deal, and in August [Novartis added Arzerra to its license for another \\$1 billion, gaining its right to treat](#) multiple sclerosis and other auto-immune conditions.

The ability to add indications beyond an initial orphan indication allows more patients to benefit from a new drug, and improves developer ROI. Rituximab, for example, originally was approved for Non-Hodgkin's Lymphoma in 1997. It was approved for rheumatoid arthritis in 2006, and [in 2011 it received Orphan Drug status \(and market exclusivity\) for Wegener's granulomatosis and microscopic polyangiitis, two rare disorders that cause vasculitis](#). Rituximab is now a blockbuster, [with almost \\$9 billion in global revenues in 2013, and double-digit sales growth in 2014](#).

Further, drug developers that wish to take advantage of the benefits of APs must also keep in mind the requirement of payers. Although payers in the U.S., Europe, and Japan all are looking for value to be clearly demonstrated, and communicated, the details that determine that value may vary.

To succeed in Europe, developers must strive to engage as early as possible with HTAs, as reimbursement is highly dependent upon the determination of economic benefit by the HTAs. Individual national HTAs may make different assessments of benefit, influenced by the state of their country's economy. A nation with a troubled economy may be more reluctant to reimburse a costly drug than one with a more robust one. And even among richer countries, there are differences in emphasis. For example, Nordic countries tend to calculate the impact of a new treatment's societal impact on health system costs, whereas the UK leans toward a Quality Adjusted Life Year (QALY) assessment of disease burden. (Payers in the U.S., according to a recent PAREXEL/NEHI survey, do not believe that QALY will ever be a significant metric for them.) It's therefore not surprising that, in an attempt to promote patient access to approved medicines across the EU, the EMA offers opportunities for developers to seek joint scientific advice and meetings with EMA and HTAs early in development process, whether or not a sponsor is seeking an AP designation.

The U.S. is a complicated and fragmented free market for drugs that nonetheless has a new sharp focus on drug prices and prescribing habits. Payers increasingly demand demonstration of value, especially for medicines perceived as very expensive, and may not be satisfied by the clinical evidence required by FDA for demonstrating that value. They may ask for additional clinical study, or RWE, before including a drug on their formulary. Planning ahead for this possibility is now essential for sponsors.

In Japan, regulators and government payers sit under the same roof, the Ministry of Health, Labor, and Welfare, so the dialogue among developers, regulators, and payers is more integrated. There currently is intense debate in the Japanese pharmaceutical ecosystem about the right balance between accelerating innovation, and containing health care expenses. The likely outcome is a cap on the maximum annual revenue allowed for blockbuster drugs, even if they have benefited from accelerated approval.

AP-based regulatory approval may be founded on just one critical trial, or on one surrogate endpoint. It is therefore important for sponsors to be sure their trials are appropriately designed, and the endpoint well-chosen and acceptable to the agencies from which they are seeking approval.

Ultimately, sponsor success in the evolving AP environment requires:

- Understanding the proper timing of AP designation submissions, and what is required for each. Orphan Drug or Fast Track designation can be applied for using nonclinical data (in the U.S.), although the data must be compelling. BTD requires preliminary clinical evidence, and, due to the high volume of applications, the FDA's Division of Oncology Products has been giving advice to sponsors about whether the preliminary evidence they have is potentially sufficient for BTD designation. *Sakigake* designation requires nonclinical data and early clinical data.
- Recognizing the scientific, procedural, and economic differences among target jurisdictions, and being able to reap maximum benefits from the applicable APs, as well as being able to position a new drug consistently in consideration of those differences.
- Conducting well-conceived, well-designed trials calibrated for endpoints acceptable to both regulators and payers in the different jurisdictions. For example, in oncology drugs, the EMA wants to see benefits in overall survival or progression-free survival, considering quality of life (QoL) secondarily. The FDA, on the other hand, has tended toward more symptom-specific measurements, and sees patient-reported outcomes as a secondary, rather than as a primary, endpoint.
- Creating submission documents that contain the data desired by the various agencies, presented as a compelling, easily-comprehensible value story. FDA guidance, for example, says a BTD request should be 10-to-20 pages long. However, some developers go far

beyond that, in effect "dumping data," thereby possibly causing confusion that may negatively affect a product's chances for designation. A thorough but concise, focused document that describes the anticipated benefits and risks of the drug is recommended. It is worth noting that, according to a recent PAREXEL and Network for Excellence in Health Innovation (NEHI) study, smaller (less than 250 staff) U.S. developers have only a 19% success rate with BTD applications (despite all the innovation coming out of smaller companies) compared to 44% for midsized companies and 61% for large companies. The availability of experienced resources to smaller developers may be a factor.

- Committing to providing follow-on clinical studies, and/or RWE on safety and efficacy, when applying in any jurisdiction, and making sure that the sponsor has the resources to fulfill that commitment, as AP designations can be withdrawn as well as granted.
- Rigorously assessing a sponsor's capabilities. For example, in March 2015, the [EMA recommended for Accelerated Assessment \(AA\) Lenvima](#), designed to treat adults with progressive, locally advanced or metastatic differentiated thyroid carcinoma whose disease has progressed despite the administration of radioactive iodine. After the AA was granted, the CHMP requested a further study to calibrate dosage. Accelerated Assessment, which brings review times down from 210 to 150 days, and is a boon to developers with competitors hot on their heels, requires that they respond quickly during that abbreviated period to CHMP questions, meaning they must have the resources and capabilities to do so, as well as high-quality, accessible data. If the developer cannot respond expeditiously to the CHMP's requests, the advantage of the shorter review is lost.
- Fully appreciating the different, possibly complementary, or sometimes divergent data requirements of regulators and payers in support of an AP drug that could have a high therapeutic impact and a high price. Proper and timely planning by sponsors will help mitigate delays in patient access and ROI.

Innovative medicines, and niche indications, have resulted in an increased number of APs in recent years. The forthcoming Priority Medicines (PRIME) AP, expected to be launched this year by the EMA, is indicative of the regulators' desire – in all jurisdictions – to assist sponsors in their efforts to bring new therapies to patients with little, or limited therapeutic options.

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