Several regulatory agencies, including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), have implemented regulatory pathways to expedite drug development and review for promising new therapies. Though these programs vary in several important ways, they are all intended to minimize delays in patient access to innovative treatments for serious, unmet medical needs. Over the last two decades, there have been concerted efforts to increase harmonization across these regulatory bodies and eliminate unnecessary barriers that may delay or otherwise impede the efficient development and production of pharmaceuticals. However, relatively less attention has been paid to harmonization across the expedited pathways.

As regulatory agencies move towards better harmonization, these expedited programs should be examined to identify whether variations in regulatory processes and evidentiary requirements may inhibit innovation or patient access. The purpose of today’s workshop is first to explore whether a lack of harmonization among the various expedited programs worldwide hinders or delays drug development and, if so, to explore specific areas where international harmonization or coordination could help alleviate any identified problems.

Expedited Regulatory Pathways for Drug Review and Approval

Since the early 1990s, drug regulatory agencies around the world have developed a range of strategies aimed at encouraging therapeutic innovation and enabling flexible approaches to regulatory decision-making. Among these approaches has been the establishment of expedited programs for the review and approval of drugs that target serious unmet medical needs. This section provides a brief overview of the key features and qualifying criteria for several of these pathways. (For a summary view of this information, see Tables 1 and 2.)

**Expedited Pathways at FDA**

FDA currently administers several expedited programs including priority review, accelerated approval, fast track, and breakthrough therapy designation (BTD). All of these programs are designed to facilitate the development of products that intend to treat serious conditions. However, the pathways have different eligibility requirements and corresponding features, and may be used in conjunction with each other, where appropriate, to further accelerate the development and review process.

**Priority review** was established under the Prescription Drug User Fee Act of 1992. In order to qualify, a drug candidate must treat a serious condition and, if approved, be expected to provide significant improvement over existing treatments in terms of safety and/or effectiveness. Certain categories of drugs—such as anti-infectives that have been designated by the agency as qualified infectious disease products—may be granted automatic priority review. Once granted, the FDA must review the application for approval within 6 months, rather than the standard 10-12 months.¹
The **accelerated approval** pathway was also established in 1992[^1], though under a separate regulatory authority (Subpart H of FDA’s New Drug, Antibiotic, and Biological Products regulations).[^2] In order to qualify for this approval pathway, a drug must treat a serious condition, potentially provide meaningful advantage over the available therapies for that condition, and demonstrate an effect on a surrogate or intermediate clinical endpoint that is “reasonably likely” to predict clinical benefit. Once approved, the sponsor must conduct post-approval studies to ensure that the anticipated clinical benefit has been realized, at which time the FDA may confirm full approval of the drug. The agency may also revoke its approval if new evidence emerges showing that the drug’s benefits do not outweigh the risks.

**Fast track designation** was established under section 112 of the Food and Drug Administration Modernization Act of 1997. In order to qualify, the sponsor must provide clinical or non-clinical evidence that the drug in question both treats a serious condition and addresses an unmet medical need. Drugs that qualify for this pathway are eligible to receive rolling application review, as well as earlier and more frequent communication with the agency. FDA reserves the right to rescind the designation if subsequent evidence demonstrates that the therapy no longer meets the criteria.

**Breakthrough therapy designation** (BTD), was established under the Food and Drug Administration Safety and Innovation Act of 2012.[^3] To qualify for breakthrough designation, a therapy must show early clinical evidence of substantial improvement over existing therapies on one or more clinically significant endpoint(s), in addition to treating a serious or life-threatening disease or condition. Once granted, FDA commits to providing the sponsor with timely advice and interactive communications throughout the development process. These interactions may include interim analyses of trial data, alternative proposals for smaller or more efficient trials, and rolling review of the drug’s application. The agency also agrees to allocate additional staff resources to support the review process. This includes a project lead, who serves as a scientific liaison between members of the review team and facilitates communication between the sponsor and the agency.[^4] Where appropriate, senior agency staff are included in the process. As with fast track, FDA may rescind the designation upon receipt of additional evidence or if the drug development program is no longer being pursued.

In 2016, FDA approved a total of 22 novel therapeutics. Of those approvals, eight received fast track designation, seven were designated as breakthrough therapies, 15 received priority review, and six received accelerated approval.[^5]

** Expedited Programs at the EMA**

Drugs that undergo the EMA’s standard centralized marketing authorization procedure can generally expect to receive an approval decision from the committee that oversees approvals for human medicines—the Committee for Medicinal Products for Human Use, or CHMP—withi within 210 days. (Actual standard approval timelines are typically longer, as the 210-day window does not include the time spent by sponsors preparing responses to regulatory questions.) The EMA also maintains three expedited pathways: accelerated assessment, conditional marketing authorization, and PRIority MEdicines (or PRIME).

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[^1]: An earlier version of the this pathway was formalized in 1988 in response to the AIDS epidemic, under part 312, subpart E of the Code of Federal Regulations (See Food and Drug Administration, Interim Rule, Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses (53 FR 41516, October 21, 1988).
Since 2004, drugs submitted to the centralized authorization procedure may qualify for **accelerated assessment**, which shortens the CHMP review timeline to 150 days, and is similar in intent to the FDA’s priority review program. In order to qualify, the sponsor must justify in their application that the drug is “of major public health interest”. Typically, this requires evidence that the drug in question addresses an unmet medical need “to a significant extent”. The CHMP may also decide to provide accelerated assessment of its own accord, and may at any point decide to terminate accelerated assessment and continue the assessment under the standard timeline.  

Starting in 2006, EMA began implementing the **conditional marketing authorization pathway**, which allows the CHMP to grant a conditional, annually renewable approval for drugs that meet certain criteria. In order to qualify, a drug must be aimed at treating, preventing, or diagnosing a serious or life-threatening disease; intended for emergency use; or designated as an orphan drug. Additionally, the CHMP must determine that the drug meets four key criteria: 1) based on the existing evidence, the drug’s benefits outweigh the risks, 2) the sponsor will be able to collect comprehensive post-market data, 3) the drug fulfills an unmet medical need, and 4) the benefits of its immediate availability outweigh the risks associated with approving it with more limited data. Similar to FDA’s accelerated approval process, the sponsor must continue to collect post-market data on the drug to confirm its benefit. The authorization may be converted to a standard approval once sufficient data is available, or revoked if it is determined that the drug’s benefits do not outweigh its risks. In certain exceptional circumstances, EMA may also grant conditional authorization for a therapy that does not have comprehensive data on safety and efficacy (referred to as “authorization under exceptional circumstances”). This may occur when the condition or disease to be treated is very rare, or collection of full information is either not possible or would be considered unethical.

The **PRIME scheme** was introduced in 2016, and is similar to BTD in several key respects. Like BTD, PRIME fosters frequent and early interaction between sponsors and regulators, and is aimed at improving trial design and streamlining the development process. Sponsors whose product has been approved under the PRIME pathway benefit from a designated CHMP liaison, early feedback on development and regulatory strategy, and scientific advice when certain development milestones have been met. While large pharmaceutical companies are eligible for PRIME following proof-of-concept trials, smaller companies and academic groups—which would particularly benefit from earlier scientific consultation and advice—can apply at an earlier stage, on the basis of compelling non-clinical and tolerability data from initial clinical trials. The PRIME scheme also enables the CHMP to proactively identify eligible medical products. 

Between March of 2014 and August of 2016, EMA also piloted a fourth expedited program, known as the **adaptive pathways** approach. (A final report assessing the pilot was published in July 2016.) The adaptive pathways approach builds on the existing regulatory framework—specifically conditional market authorization—and is not a new regulatory pathway. Rather, it is an approach to regulatory decision-making that relies on three principles: 1) an iterative development and approval process; 2) a reliance on real-world data, (encompassing both prospective and retrospective observations of clinical practice); and 3) early and ongoing involvement of patients and HTA bodies. The pilot was targeted towards products that addressed areas of high unmet medical need, particularly diseases where it is difficult to conduct randomized clinical trials (e.g., Alzheimer’s disease, infectious diseases, and rare cancers). Of the 62 product applications for the pilot program, seven were accepted. Six of the accepted products were selected for parallel regulatory-HTA scientific advice and one was selected for formal scientific advice. Though the adaptive pathways pilot has ended, EMA is continuing to explore
the concept in the context of parallel scientific advice with HTA bodies and other stakeholders, such as patients and payer organizations.\textsuperscript{14}

In 2016, the EMA approved three drugs under the conditional marketing authorization, and designated a total of 20 products under the PRIME pathway.\textsuperscript{15, 16} Twelve products were accepted under the accelerated assessment pathway.\textsuperscript{17}

**Expedited Programs at PMDA**

PMDA (working closely with the Ministry of Health, Labour and Welfare, or MHLW) maintains three expedited pathways: priority review, Sakigake, and a conditional and time-limited approval scheme targeted at regenerative therapies. In order to qualify for **priority review**, a drug must target a serious or life-threatening condition, and it must exhibit improved clinical usefulness over existing therapies in terms of safety, efficacy, or patient quality of life.\textsuperscript{18} Once qualified, PMDA commits to reviewing the application within nine months, rather than the standard twelve months.\textsuperscript{19}

In 2015, PMDA and MHLW instituted the **Sakigake Designation System**, which is similar in key respects to BTD and PRIME. To qualify, a therapy must meet four criteria: 1) it targets a serious or life-threatening condition, 2) it demonstrates improvement over existing therapies in terms of safety or efficacy, 3) it has a different mechanism of action than existing therapies, and 4) the sponsor intends to conduct early clinical development and submit the drug for initial regulatory approval in Japan.\textsuperscript{20} In exchange, the sponsor receives prioritized PMDA consultations, a designated contact who acts as a liaison between the sponsor and the review team throughout development, rolling review of the marketing application, and an accelerated review time of six months.\textsuperscript{21, 22}

Since 2014, the agency has also maintained a **conditional and term-limited approval scheme** specifically targeted at regenerative therapies. This pathway is similar to the FDA accelerated approval and EU conditional marketing authorization, in that it allows approval based on a surrogate endpoint(s), and the sponsor must confirm the safety and effectiveness of the therapy through post-market studies.\textsuperscript{23} The sponsor also must resubmit an application for authorization within established term limits of up to seven years.\textsuperscript{24}

As of 2016, PMDA and MHLW have approved six drug marketing authorizations under the Sakigake Designation System, and at least two regenerative therapies under the conditional regenerative therapy pathway.\textsuperscript{25, 26}

**Expedited Programs at Health Canada**

Health Canada’s **priority review** pathway is similar in intent to FDA’s priority review program and EMA’s accelerated assessment process. In order to qualify, a drug must be intended to treat a serious, life-threatening, or severely debilitating disease or condition, and there must be substantial evidence that the drug provides either: 1) an “effective treatment, prevention, or diagnosis of a disease or condition that does not have an approved drug in Canada”; or 2) it demonstrates improvement in the risk-benefit profile over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. Additionally, the drug must treat, prevent or diagnose a serious symptom or manifestation of the disease or condition.\textsuperscript{27} Once priority review is granted, Health Canada commits to issuing an approval decision within 180 days, rather than the standard review timeline of 300 days.
Advancing Harmonization across Expedited Programs

Though these expedited programs share common goals and certain key features, they are different in several respects, including their respective eligibility requirements, timelines for application and regulatory decision-making, and associated evidentiary requirements. These differences reflect a variety of factors, including differing legal and regulatory frameworks, institutional approaches to benefit-risk assessment, and population health needs. These disparities may present challenges for drug sponsors attempting to navigate the development and approval process across multiple regions, and concerns have been raised that these differences may lead to delays in drug approval or innovation. More broadly, there are concerns that differences in the review and approval of drug applications can result in undesirable disparities in clinical practice guidelines, pricing and reimbursement decisions, and patient access.

Since its establishment in 1990, the International Council for Harmonisation has developed a range of guidelines aimed at aligning global standards for safe, effective, and high quality drugs and biologics. While these guidelines address cross-cutting areas of interest, such as good manufacturing practices, pharmacovigilance, and statistical practices for clinical trials, they do not address specific regulatory pathways. FDA and EMA have recently taken steps to facilitate parallel discussions between the two agencies for medicines designated under both PRIME and BTD, but these discussions do not explicitly cover medicines that are eligible under other designations.

Where appropriate and in line with existing legal and regulatory frameworks, increased harmonization of procedural and evidentiary requirements may minimize redundancies in clinical trial research, cut drug development costs, facilitate pharmaceutical innovation, and improve coordination and communication between different regulatory authorities. Further input from key stakeholders may help to identify areas where harmonization would be of greatest value.

Workshop Objectives

In light of these issues, and under a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy will hold a half-day private workshop composed of representatives from international regulatory bodies, industry, academia, non-governmental organizations, and patient advocacy groups. Discussion over the day will include a review of the expedited programs overseen by select regulatory agencies, and will seek to identify whether a lack of harmonization among the various expedited programs hinders or delays drug development. Discussion will extend to where opportunities exist for expanding patient access to innovative therapies through increased harmonization of these programs. Specific questions to address through presentations and moderated discussion include:

- How and to what extent is a lack of harmonization across the expedited programs of various regulatory agencies adversely affecting drug development?
- To what extent do differences in process requirements across the various regulatory agencies’ expedited programs lead to delays in approval? (e.g. differences in timing of application and review timelines, eligibility criteria)
- To what extent is lack of alignment across the agencies’ scientific advice leading to delays in approval? (e.g. differences in acceptable endpoints, trial design, number of trials required, safety population) Are there particular contexts in which better alignment is important?

† The views expressed in written workshop materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsements by the U.S. Government.
• Are there additional issues related to the design or implementation of expedited pathways that may contribute to delays in patient access? (e.g., issues related to lack of harmonization or alignment between regulator and payer evidentiary needs, delays in emerging market regulatory approval)

• What are some possible solutions for addressing stakeholder concerns with these issues?


26 Nagai, S., & Ozawa, K. (2016, April 15). Regulatory approval pathways for anticancer drugs in Japan, the EU and the US. International Journal of Hematology, pp. 73-84.


