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REGULATORY STATEGIES FOR EXPIDITED DRUG APPROVAL OF US, EUROPE AND JAPAN

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ABSTRACT

The increasing demand for rapid access to innovative therapies has driven the development of regulatory strategies that expedite drug approvals while upholding safety and efficacy standards. Regulatory agencies like the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) have introduced expedited pathways, including Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval in the U.S., as well as similar programs such as Japan's Sakigake Designation System and Conditional Early Approval. These initiatives aim to reduce review times and allow patients to access promising treatments sooner, especially for serious and rare conditions. Moreover, adaptive licensing and the incorporation of real-world evidence further improve the approval process's efficiency. However, while these expedited approvals offer benefits, they also present challenges, including limited data before market entry, the need for post-marketing surveillance, and potential safety issues. This review examines the main regulatory strategies, their effects on drug development, and the need to balance quick access with patient safety.

INTRODUCTION

The drug development process is a demanding and lengthy process, with extended lead times and a poor success rate for clinical trials, in which merely some 10% of the compounds make it past phase I. This is still the case even after numerous scientific guidelines have been released, meetings and discussions with regulators, and establishment of individual review timetables by regulatory agencies across different countries. Fortunately, regulatory agencies across the globe are leveraging new science to allow faster approval of new drugs that promise hope to patients in the therapeutic areas that are still under-served by medicine. Through the use of new trial designs, new endpoints, new data sources such as patient-generated data, and improved communication between sponsors and regulators, expedited programs are closing the gap between drug companies and patients who need these drugs.[1]

In the United States, the Food and Drug Administration (FDA) has established four main expedited programs: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review. The Accelerated Approval program allows drugs to be approved based on surrogate or intermediate clinical endpoints, but it requires post-marketing confirmatory trials to validate long-term benefits. [2]

The European Medicines Agency (EMA) offers Conditional Marketing Authorization (CMA) for medicines that meet unmet medical needs, permitting early approval while evidence continues to be gathered. Additionally, the Priority Medicines (PRIME) initiative encourages early regulatory engagement to speed up the development of promising therapies. The Accelerated Assessment process shortens the standard 210-dayreview period to 150 days for drugs that provide significant therapeutic advancements.[3]

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) has the Sakigake (Pioneering) Designation, which allows for priority consultations and reduced review times for innovative treatments. Japan also implements the Conditional Early Approval System, which grants provisional approval for drugs targeting serious or rare diseases, akin to the FDA's Accelerated Approval.[4]

DEFINITION

The **expedited drug approval process** refers to a set of regulatory pathways designed to accelerate the development, evaluation, and approval of drugs intended to treat serious or

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life-threatening conditions, particularly when there is an unmet medical need. [5]

These pathways enable faster access to innovative therapies by allowing the use of surrogate endpoints, rolling reviews, and prioritized evaluations while maintaining safety and efficacy standards.

HISTORY AND EVOLUTION OF EXPEDITED APPROVAL

- **1962 – Kefauver Harris Amendment**: Established stricter drug approval processes following the thalidomide scandal, ensuring that drugs must demonstrate both safety and efficacy before approval.
- **1976 – Group C Cancer IND Program**: Allowed oncologists to provide investigational cancer drugs outside clinical trials, leading to the FDA's first official Expanded Access policy in 1979.
- **1980s – The AIDS Crisis**: Patient advocacy efforts pushed the FDA to create more formal compassionate use pathways, expanding access to investigational drugs for life-threatening diseases.
- **1987 – Investigational New Drug (IND) Expansion**: Introduced three categories for investigational drugs: Investigator IND (for physician-led studies), Emergency IND (for urgent cases), and Treatment IND (for promising drugs for serious conditions).
- **1988 – Fast-Track Program**: Implemented to expedite drug development for life-threatening conditions by allowing developers to defer or bypass Phase 3 clinical trials.
- **1992 – Accelerated Approval**: Allowed drug approval based on surrogate endpoints (e.g., biomarker data) rather than traditional clinical outcomes, reducing the time required for approval. [6]

REGULATORY FRAMEWORK AND GOVERNING BODIES

Expedited drug approval is governed by regulatory agencies that establish guidelines and oversee the approval process to balance innovation with public safety. The key governing bodies and their expedited approval pathways include:

- **U.S. Food and Drug Administration (FDA)**: Implements Fast Track, Accelerated Approval, Priority Review, and Breakthrough Therapy Designation to facilitate quicker access to essential drugs.
- **European Medicines Agency (EMA)**: Oversees Conditional Marketing Authorization and PRIME (Priority Medicines) designation to support early patient access to critical treatments in the European Union.
- **Japan's Pharmaceuticals and Medical Devices Agency (PMDA)**: Regulates expedited drug approvals through the Sakigake designation system, designed for innovative and urgent medical needs.
- **World Health Organization (WHO)**: Provides global guidance and supports regulatory harmonization across different countries to improve access to essential medicines through prequalification programs.

METHODS

Generally, the following regulatory options are available globally to expedite the development and approval of innovative drugs in areas of serious and life-threatening diseases and unmet medical need:

DECREASING DRUG DEVELOPMENT TIMELINES

This method involves increased frequency of interactions starting early and continuing throughout drug development and involves designations as Breakthrough and Fast Track in the US or Priority Medicine (PRIME) in the EU.

DECREASING APPLICATION REVIEW TIME

These pathways are intended to shorten the regulatory review timelines by health authorities. Regulatory agencies provide additional resources to expedite the review and evaluation of regulatory submissions. This includes pathways such as Priority Review in US or Accelerated Assessment in the EU.

PRELIMINARY APPROVAL PENDING ADDITIONAL DATA

In most countries, this pathway includes regulatory approval based on a surrogate or early endpoint. Approval through this pathway needs to be complemented by further clinical data generated post-authorization as laid out in commitments, such as Accelerated Approval in US or Conditional Marketing Authorization in the EU. [7]

US – EXPIDITED DRUG APPROVAL

Speeding up the approval of drugs for the treatment of serious disease is in the public interest, particularly when drugs are new for their class or an advance over existing therapies. The Food and Drug Administration has adopted four new and innovative approaches to make these drugs available as quickly as possible to patients:

FAST TRACK

Fast Track Designation is an FDA initiative designed to accelerate the development and review process for drugs targeting serious conditions that lack effective treatments, ensuring that vital new therapies are available to patients more quickly.

Key Features:

- Focus on Serious Conditions – This includes illnesses such as cancer, Alzheimer's, heart failure, AIDS, epilepsy, depression, and diabetes.
- Addressing Unmet Medical Needs– The drug must either:
- Introduce a new treatment where none is available.
- Provide a significant improvement over current therapies (for instance, enhanced effectiveness, reduced side effects, or better diagnostic capabilities).

Benefits of Fast Track Designation:

1. Increased FDA Interaction & Guidance – This helps ensure the study design and data collection are appropriate.
2. Rolling Review – Companies can submit sections of their application for review rather than waiting to com-

plete the entire application.

3. Potential for Accelerated Approval & Priority Review – If the criteria are satisfied, the drug may be eligible for even quicker approval.

How to Apply?

- A pharmaceutical company must formally request Fast Track designation.
- The FDA will evaluate the request within 60 days to determine if the drug qualifies.

Why It Matters?

Fast Track helps minimize delays in drug approval by enhancing communication between the FDA and drug developers, enabling patients to gain access to promising new treatments sooner. [8]

BREAKTHROUGH THERAPY

Breakthrough Therapy is an FDA program designed to speed up the development and review of drugs that demonstrate strong early evidence of significantly improving treatment for serious conditions.

Key Criteria

- The drug must treat a serious disease (such as cancer, Alzheimer's, or genetic disorders).
- Early clinical evidence must indicate major improvement over existing treatments.
- The improvement can be in:
- Survival or quality of life (reducing irreversible morbidity or mortality).
- Effectiveness on biomarkers that suggest clinical benefit.
- A better safety profile (fewer severe side effects).

Benefits of Breakthrough Therapy Designation:

- All Fast Track benefits, including Rolling Review.
- Early and intensive FDA guidance (starting as early as Phase 1 trials).
- High-priority attention from senior FDA officials.

How to Apply?

- A drug company must request Breakthrough Therapy designation.
- The FDA may suggest a request if it identifies strong potential.
- The request should be submitted by the end of Phase 2 trials to maximize benefits.
- The FDA reviews the request within 60 days.

Why It Matters?

Breakthrough Therapy accelerates the approval process, enabling patients to access life-saving treatments more quickly. [9]

ACCELERATED APPROVAL

1. Purpose of Accelerated Approval

Evaluating new drugs typically takes several years to establish a clinical benefit, which refers to how much a drug enhances survival, well-being, or daily functioning. To expedite this process, the FDA introduced Accelerated Approval in 1992, enabling certain drugs to gain approval more quickly based on early signs of effectiveness (surrogate endpoints) instead of waiting for complete clinical outcomes.

2. Legal Framework

In 2012, the Food and Drug Administration Safety Innovations Act (FDASIA) was passed. Section 901 of FDASIA modified the Federal Food, Drug, and Cosmetic Act (FD&C Act) to permit accelerated approval based on: Surrogate endpoints-laboratory tests, imaging results, or physical signs that indirectly indicate a drug's benefit. Intermediate clinical endpoints-metrics that are reasonably likely to predict a significant clinical outcome, such as reducing irreversible morbidity and mortality (IMM).

3. How the FDA Evaluates Surrogate and Intermediate Endpoints

The FDA thoroughly reviews the scientific evidence backing these endpoints. Approval hinges on "adequate and well-controlled" clinical studies that demonstrate a positive effect on the selected endpoint.

4. Advantages of Accelerated Approval

This pathway can significantly shorten the time it takes for drugs to be approved, facilitating quicker access to life-saving treatments. For instance, rather than waiting years to see if a cancer drug improves survival rates, the FDA might grant earlier approval if it shows tumor shrinkage, which is often a strong predictor of long-term survival benefits.

5. Post-Approval Requirements

After approval, confirmatory clinical trials must be conducted to verify that the surrogate endpoint genuinely translates into a tangible clinical benefit. If these trials confirm the anticipated benefit, the FDA will lift the requirement for additional studies. Conversely, if the trials do not confirm the benefit or uncover safety issues, the FDA may: withdraw the approval or modify the drug's labeled indication, limiting its approved uses.[10]

PRIORITY REVIEW

Before a drug can be approved for use in the United States, it must go through a thorough FDA review process to assess its safety, effectiveness, and overall benefits. To enhance the efficiency of this process, the Prescription Drug User Fee Act (PDUFA) was enacted in 1992, creating a two-tiered review system:

1. Standard Review-The FDA reviews the drug within 10 months.

2. Priority Review-The FDA expedites the review, aiming to make a decision within 6 months.

What is Priority Review?

Priority Review is assigned to drugs that have the potential to substantially enhance the treatment, diagnosis, or prevention of serious conditions compared to existing therapies. This designation does not change the approval standards but ensures that the FDA dedicates more resources to the review process.

Criteria for Priority Review

A drug may be eligible for Priority Review if it demonstrates:

- All Fast Track benefits, including Rolling Review.
- Enhanced effectiveness in treating, diagnosing, or preventing a condition.
- Reduction or elimination of serious side effects that limit treatment options.
- Improved patient compliance, resulting in better health outcomes.
- Evidence of safety and effectiveness in a previously untreated subpopulation.

How is Priority Review Granted?

- The FDA decides the review designation for each application.
- A drug sponsor can formally request Priority Review following FDA guidelines.
- Within 60 days of receiving a Biologics License Application (BLA), New Drug Application (NDA), or efficacy supplement, the FDA informs the sponsor of its decision.
- This designation does not influence the duration of clinical trials or the level of evidence needed for approval. [11]

EUROPE- ACCELERATED ASSESSMENT

Accelerated assessment is an accelerated review procedure employed by the European Medicines Agency (EMA) to expedite the evaluation timeline for marketing-authorization applications. It is awarded if a medicine is found to be of significant public health interest and provides considerable therapeutic innovation.[12]

Standard assessment: The CHMP reviews an application in 210 days, excluding "clock stops" should additional information be requested from the applicant.

Accelerated assessment: Depending on sufficient justification by the applicant, the review period can be shortened by the CHMP to 150 days.

Purpose Of Accelerated Assessment

This mechanism is intended to accelerate the availability of significant medicines, specifically those that treat unmet medical needs or make substantial treatment advances. It still does guarantee careful scientific review of safety, quality, and effectiveness of the medicine.

How to Apply

1. Time of Request

- Requests for accelerated assessment need to be submitted two to three months at least prior to submission of the marketing-authorization application.
- It is advised that early interaction with the procedure manager of the EMA take place to secure an efficient and timely submission.

2. Pre-Submission Meeting

- EMA highly recommends that applicants seek a pre-submission meetingsix to seven months prior to submitting their application.
- Applicants can use this meeting to address their proposal for accelerated assessment with:
- CHMP (Committee for Medicinal Products for Human Use)
- Other concerned committees, e.g., the Pharmacovigilance Risk Assessment Committee (PRAC) or the Committee for Advanced Therapies (CAT)
- The data package and risk management plan can also be submitted by the applicants for consideration.

3. Request Submission

- The request for a pre-submission meeting must be made electronically to EMA with supporting documents.

4. Prime scheme

- Since March 2016, EMA's PRIME (PriorityMedicine's) schemeenables applicants to get early notification during clinical development as to whether their medicine could be eligible for accelerated assessment.
- This aids applicants in having an effective submission strategy and enables quicker access to ground-breaking treatments.

JUSTIFYING ACCELERATED ASSESSMENT

- Candidates must justify why their medicinal product is going to be of major public health significance, particularly with regard to therapeutic innovation.
- For more specific eligibility requirements, candidates can consider the pre-submission guidancequestion: Is my product eligible for an accelerated assessment?

PRE-AUTHORISATION INSPECTIONS

- The EMA is required to make sure that the manufacturers and the submitted studies are in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP).
- The applicants should provide the applicant with GMP and GCP relevant information in such a way that any inspections to be included within the accelerated assessment are mentioned.
- If the inspection is required, it will be sought as early as possible during the evaluation.

For more information, refer to the pre-submission questions:

- Is my product eligible for an accelerated assessment?
- When will I have a pre-approval GCP inspection and how is it conducted?
- When will I have a pre-authorization GMP inspection and how is it conducted?

How to Submit a Request for Accelerated Assessment

1. Submit via EMA Service Desk

- Select 'Business Services' → 'Human Regulatory'
- Select 'Pre-Submission Phase - Human' → 'Accelerated Assessment Request'

2. EMA Account Requirement

- If the applicant does not have an EMA account, one needs to be created via the EMA Account Management portal

- Instructions on how to open an account may be seen in the document Create an EMA Account.

3. Pre-Submission Request Form

- A particular pre-submission request form is needed prior to submitting a **marketing authorization applicationor Article 58 Application.

Assessment Procedure

- When the rapporteurs receive the request, they prepare a briefing note with their recommendations.
- The CHMP considers the request in terms of:
- The grounds put forward
- The rapporteurs' recommendations
- Where clarifications are needed, the CHMP may request these of the applicant.
- The result of the final opinion is communicated to the applicant, along with the reasons for approval or rejection, which are also documented in the CHMP assessment report.

Consequence on Marketing Authorization

- The CHMP opinion on accelerated assessment does not affect the final opinion as to whether or not the medicine will be authorized to market.
- If it is to be given accelerated assessment, the CHMP follows the standard 150-day review schedule.
- Accelerated treatments may have a different schedule.

Legal Basis

The procedure of accelerated assessment that is required is based on Recital 33 and Article 14(9) of Regulation (EC) No 726/2004.

Related Guidance & Documents

- Guideline on the scientific application and practical arrangements for accelerated assessment
- Pre-submission request form (PDF, 3.8 MB, Last updated: 17/12/2024)
- Request for accelerated assessment template (DOCX, 150.43 KB, Last updated: 17/02/2021)

Contact Point

In case of any questions, applicants are advised to send these through the EMA online form:

[Send a question to the European Medicines Agency](https://www.ema.europa.eu)

JAPAN

The Japan fast-track approval is intended to fast-forward approval of innovative or critically needed drugs, especially those against life threatening or severe illnesses. Different avenues under the Pharmaceuticals and Medical Devices Agency (PMDA) and the Ministry of Health, Labour and welfare (MHLW) exist.

ACCELERATED REGULATORY PATHWAYS

1. Special approval for emergency

A state of emergency requires that a non-approved healthcare product be used so that the harm in the public health caused by the spread of diseases would be avoided. The emergency situation can be managed in no way other than the use of the non-approved product. Legally available in a country whose regulation of medical products is as good as Japan's.

1. **Emergency approval**

Emergency condition requires the application of an unapproved drug in a bid to prevent danger to the public health due to the spread of diseases. This emergency situation cannot be addressed in an effective way by any other means except by utilizing the unapproved drug. Confirmed safety and estimated efficacy

2. **SAKIGAKE (Forerunner designation)**

Innovative medical products for serious diseases. Development & NDA in Japan: being world's first or simultaneous with other countries. Prominent effectiveness expected on non-clinical and early phase clinical studies

3. **Conditional early approval**

Japan's "Conditional Early Approval" program permits temporary approval of new drugs for a period of up to seven years, especially for serious diseases where full trials, e.g., Phase 3 trials, are not feasible. This is either because of limited patient population or recruitment problems in studies. Early clinical trials have to show a high degree of efficacy and safety to be eligible. The review period is reduced to nine months, allowing quicker access to vital treatments. Additionally, drugs approved under this program can be marketed in Japan with minimal trial data while further studies are ongoing even if the drug is still under development elsewhere. As such drugs are also becoming eligible for reimbursement, this program is a big boon in getting important medicines to Japan sooner.

4. **Priority review**

In Japan, as in other places that offer priority review, the requirement for this pathway is that there is no approved therapy for the disease or that the drug under investigation has demonstrated greater clinical benefit compared to approved drugs available. The greatest benefit of priority review, Lane said, is that review time is shortened to nine months from the typical 12 months.

5. **Orphan drug designation**

The treatment of any disease that affects fewer than 50,000 people, or up to 180,000 for intractable diseases of unknown origin to be treated for a prolonged duration of time. The drug must have a serious unmet medical need and a high likelihood of the success of development. The benefits are high prices, lower user fees, tax credits, and possible subsidies. The review period is shortened from 12 to 9 months, and the re-examination periodis extended to 10 years, protecting market exclusivity. This time frame offers continuous monitoring of safety and efficacy while blocking competition from other companies. [13]

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