ORIGINAL RESEARCH

COMPARISON OF THE EXPEDITED PROGRAMS & ORPHAN DRUG DESIGNATION IN THE USA & JAPAN

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ABSTRACT:

Expedited Approval Pathways and Programs for drugs, biologics or medical devices were established for rapid commercialization of innovative products in the United States of America (USA) and Japan due to an increased number of serious conditions, which demanded the development of expedited programs globally. This paper models the contrast between the U.S. and Japan's available expedited programs for faster drug development. The U.S has Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval and Priority Review Designation while Japan has Priority Review Designation, Sakigake Approval and Time-Limited approval scheme targeted at regenerative therapies. All 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.

Our research and findings indicate that 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, where payers can demand additional clinical studies, or real-world evidence. In Japan, regulators and government payers both are covered under the Ministry of Health, Welfare, and Labor, thus making the whole process more integrated. We also compare and contrast the Orphan Drug Designation in both these countries. Although similarities exist, the criteria and processes for designation are not internationally harmonized, and this editorial summarizes orphan drug designation in the USA and Japan.

KEYWORDS: Regulatory approval; Expedited-Approval Pathways; Fast Track Designation; Breakthrough Therapy Designation; Priority Review; Expanded Access; Accelerated Approval; Regenerative medicine products; pew-marketing; post-marketing; unmet medical needs

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INTRODUCTION:

Serious medical needs request the further development of innovative pharmaceutical products as well as treatment alternatives[2]. Various expedited programs to the standard review processes have been developed for faster review and quicker commercialization of the innovative products, and an increased access to the patients in need. Of the list of the expedited pathways, each of those contradicts one another in some way. Few of those require the submission of the clinically significant data which depicts the safety & efficacy of the product, before the commercialization in the standard review process, while some of the pathways do not. The pathways that do not require the submission of the clinical data before the marketing will have to submit the post-marketing clinical study data to the respective authorities[8]. Expedited programs were initiated in the 1990's in the US which includes Fast Track Designation, Breakthrough Therapy Designation, Accelerated Approval & the Priority Review, with the latest addition being the Expanded Access Designation[1].

As of late, the Japanese government has reformed their pharmaceutical affairs law, which supervises all the pharmaceutical products and the medical devices; it was named the Pharmaceuticals, Medical devices, and other Therapeutic Products Act (PMDA) in November 2014[2]. They also included regenerative medicine products as a different category from conventional pharmaceuticals. The Japanese agency has launched a pathway named Sakigake in 2015, which basically focuses on shortening the review period and eventually the approval time for the drug. This encourages the industries to turn innovations into new drugs that could treat the serious diseases and also accelerating access to unapproved and off-label drugs for serious and life-threatening diseases, including drugs not yet approved outside Japan[1].

There are estimated to be between 6000 and 8000 rare diseases. Although by definition each rare disease affects a relatively small number of patients, collectively rare diseases represent a considerable health burden. Patients with rare diseases are entitled to expect the same quality of treatment as other patients with the more common disease. Medicines and medical devices for patients with rare diseases are clinically very important. However, the lack of the attraction for developing these medicinal products, due to a small numbers of targeting patients makes it difficult to produce favorable research and development. So, in order to support the patients with rare diseases, it is necessary to establish proper measures to promote research and development for orphan medicinal products. A supportive legislative framework for medicines for rare diseases was adopted in the USA in 1983 (the Orphan Drug Act (ODA)), and in Japan in 1993 (amended Pharmaceutical Affairs Law). The criteria and processes for Orphan Drug Designation are not internationally harmonized, and this editorial focuses on key designation features in the USA and Japan[11,12].

Expedited Approval Pathways and Programs:

In the U.S., Accelerated Pathways include **Fast Track (FT), Breakthrough Therapy Designation (BTD), Accelerated Approval (AA), and Priority Review (PR) (Refer Table 1)**. And although the Orphan Drug Pathway is not APs 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.

PMDA (working closely with the Ministry of Health, Labor, and Welfare, or MHLW) maintains three expedited pathways: **Priority Review, Sakigake, and a Conditional and Time-Limited Approval scheme targeted at regenerative therapies**.

METHOD:

As the title suggests, we are comparing the new expedited programs of Japan with those already existing in the US, We have selected 7 pathways and programs in the US and Japan, of which 4 are under the agency of the US (FDA), and the others being under the agency of Japan (MHLW). All regulation documents related to expedited approval were obtained from websites of the respective authorities: the FDA (US Food and Drug Administration) and the Pharmaceuticals and Medical Devices Agency (PMDA). Prerequisites needed for collection of the post-marketing clinical data were identified from the guidance documents. The pathways and the programs were later categorized based on the requirement of pre/post-marketing data requirements, and evaluation of the post-marketing data[2].

Types of Pathways & Designations in the US:

1. Fast Track Designation
2. Breakthrough Therapy Designation
3. Accelerated Approval Pathway
4. Priority Review
5. Expanded Access

Types of Pathways & Designations in Japan:

1. Sakigake Approval
2. Conditional & Time Limited Approval
3. Priority Review

- **Fast Track Approval:**

Fast Track is a process intended to encourage the development and expedite the review of the drugs to treat the unmet medical needs. Determining a condition is serious or not is a matter of judgment, yet for the most part depends on whether the medication will affect such factors as survival, day-to-day functioning, or the probability of the condition, if left untreated, will advance to a more serious condition from a less serious state. Filling an unmet medical need or a serious condition means providing with a therapy where none exists or providing with a therapy that is better than the available therapy[7].

As addressed, any drug which is developed for a condition with no current therapy is directed at an unmet medical need; on the other hand, if there are available therapies, the drug has to have some advantages outweighing it from the available therapies[4].

✓ The advantages could be such as:

- Increased effectiveness
- Decreased side effects or
- Improved effect on the serious outcomes
- Improving the diagnosis of the serious condition
- Decreasing significant toxicity of the drug[7]

✓ Some key feature of fast track designation:

- Frequent meetings with the FDA to discuss the development plan of the drug and the

collection of data needed to support the approval
- Frequent communication with the FDA about the design of the clinical trials proposed and also the viewpoint on the use of biomarkers
- Rolling Review; means to submit the completed sections the BLA or NDA for the review by FDA[7]

The drug company can request for the fast track approval at any time during the drug development process. FDA reviews the request and makes a decision within the next sixty days if the drug fulfills the criteria of unmet medical need.

- **Breakthrough Therapy Designation(BTD):**
Breakthrough Therapy Designation is a process designed to expedite the development and review of drugs that are intended to treat a serious medical condition and preliminary clinical evidence indicates that the drug may demonstrate the substantial improvement over the available therapy on a clinically significant endpoint.
To determine if the improvement over the available therapy is substantial is a matter of judgment and depends on the magnitude of the therapy, which includes the duration of the effect and also the observed clinical outcome. Basically, the new treatment with its preliminary clinical evidence shows a clear superiority over the available therapy[4].
For BTD, the clinically significant endpoint refers to the endpoint that measures the effect on the irreversible morbidity or mortality (IMM) or on the symptoms that represents the serious consequences of the disease[7].

✓ A clinically significant endpoint can refer to the findings that suggest an effect on IMM, including,
- Effect on an established surrogate endpoint
- Effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit
- Effect on pharmacodynamics biomarker, which suggests the potential for a clinically meaningful effect on the disease
- Significantly improved profile over the available therapy[7]

✓ Some key feature of fast track designation:
- All the features as that of the Fast Track Designation
- Intensive guidance from the FDA on drug development program as early as phase 1
- Organizational commitment involving the senior managers[7]

The drug company can request for BTD. If the company has not requested BTD, then the FDA suggests the sponsor consider a request if:

- After reviewing the submitted data and information, the agency thinks that the drug development program may meet the criteria for BTD and
- The remaining drug development program can benefit from the designation[7].

The request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. The agency responds in the next sixty days after the receipt of the request.

- **Accelerated Approval:**

FDA may grant Accelerated Approval to a product for a serious or life-threatening disease or condition, upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefits, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments[4,6].

✓ Qualifying criteria for Accelerated Approval:
- Serious condition,
- A meaningful advantage over the available therapy,
- Demonstrates an effect on an endpoint that is reasonably likely to predict the clinical benefit[6].

✓ Accelerated Approval endpoints:
There are two types of endpoints that can be used as a basis for accelerated approval is
- A Surrogate endpoint that can predict the clinical benefit
- A Clinical endpoint that can be measured earlier than IMM than is reasonably likely to predict the clinical benefit[6]

✓ Evidentiary criteria for Accelerated Approval:
- Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval. Copies of all the promotional materials
- For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations
- For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling[6].

✓ Conditions of Accelerated Approval:

Promotional materials: Applicant must submit to the agency, copies of all the promotional material during the preapproval review period for consideration, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following the marketing approval. After 120 days following marketing approval, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Confirmatory trials: For all the drugs granted Accelerated Approval, the post-marketing confirmatory trials have been required to verify and describe the anticipated effects on IMM. The protocol for the post marketing trial should be developed as early as possible, and timelines for the trial should be specified; for example, timelines for enrollment and trial completion should be stipulated. There should

be an agreement between FDA and the sponsor on the design and conduct of the confirmatory trial. Generally, the confirmatory trial would evaluate the clinical endpoint that directly measures the clinical benefit.

Withdrawal of Accelerated Approval: FDA may withdraw the approval of a drug or indication approved under the accelerated approval pathway if,

- A trial required to verify the predicted clinical benefit of the product fails to verify the clinical benefit
- Other evidence demonstrates that the product is not shown to be safe or effective under conditions of use
- The applicant fails to conduct any required post-approval trial of the drug with due diligence
- Applicant disseminates false or misleading promotional materials relating to the product[6]

- **Priority Review:**
  If an application for a drug will receive a Priority Review Designation if it is a drug that treats a serious condition and if, approved would provide a significant improvement in the safety or effectiveness. In priority review, the FDA directs all the attention as well as the resources for evaluation of such applications[6].

  Criteria for Priority Review Designation:

- Serious condition
- Demonstrating the potential to be a significant improvement in safety or effectiveness, It can be demonstrated by:
  - Evidence of increased effectiveness in treatment, prevention, or diagnosis of the condition
  - Elimination or substantial reduction of a treatment-limiting drug reaction
  - Documented enhancement of patient compliance that is expected to lead an improvement in serious outcomes or
  - Evidence of safety and effectiveness in a new subpopulation[7]

✓ Features:
- An action is taken by the FDA within the next six months of the receipt (compared to ten months of standard review)
- FDA informs the applicant about the Priority Review Designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement[4].

- **Conditional & Time Limited Approval:**
  Since 2014, the agency has also maintained a conditional and Time-Limited Approval scheme specifically targeted at regenerative therapies. This pathway is similar to the FDA Accelerated Approval**,** 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. The sponsor also must resubmit an application for authorization within established term limits of up to seven years[3].

  Ways to expedite R&D for the Conditional & Time-Limited Approval:

- Designed for unmet medical needs
- Conducting a controlled study to demonstrate "true endpoint" of clinical benefit
- Heterogeneity of quality affected by source materials[3]

The Conditional and Time-Limited Approval, specifically for regenerative medicine products is normally difficult to evaluate efficacy due to the considerable variation caused by the different donors or cells. Therefore, Conditional and Time-Limited Approval requires confirmation of safety and demonstration of probable benefit. Demonstration of probable benefit can be done by data that predicts efficacy through surrogate endpoints in a relatively small exploratory study. After Conditional and Time-Limited Approval, it is necessary to conduct patient follow-ups to further confirm safety and efficacy. Application forms for Conditional and Time-Limited Approval are the same as regular approval. Thus, during the review, the PMDA and MHLW will decide whether which type of approval is appropriate. It is required to apply for regular approval under article 23–25 of the PMD Act within the specified period (normally maximum 7 years) following Conditional and Time-Limited Approval, the approval will expire thereafter[3].

New Scheme for Regenerative Medicines:

1. Clinical study
2. Clinical Trials (likely to predict efficacy, confirming safety)
3. Conditional/Term-limited Authorization
4. Marketing for further safety and efficacy
5. Marketing Authorization or Revocation (Simultaneously, one can also apply for Re-marketing which is maximum up to 7 years)
6. Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risks to patients during step 4-6.

In September and in October 2014, two new product applications for marketing authorization were filed by PMDA. They were approved on September 18, 2015.

- Bone Marrow Mesenchymal Stem Cells (MSCs) for GVHD. (Normal Approval) - TEMCELL
- Skeletal Myoblast Sheet for serious heart failure due to ischemic heart disease. (Conditional and time-limited authorization – 5 years, conducting post-marketing efficacy studies where the review time was less than 12 months). – HEARTSHEET

- **Challenges:**

1. Clinical Study in Post-marketing
2. Reimbursement
3. CMC and Quality Assurance

- **Priority Review:**
  Drug approval review are normally processed in the order that the application forms are received, but for the drugs designated as orphan drugs and other drugs considered to be especially important from a medical standpoint such as new drugs for serious condition, a decision must be made whether or not to specify an overall evaluation of:
- The seriousness of the targeted disease and
  - The clinical usefulness[3]

Within this system, the application is reviewed on a priority basis.

Criteria for the priority review:

- Seriousness of indicated diseases
- Disease with important effects on patient's survival
- Progressive and irreversible diseases with marked effects on daily life
- Other
- Overall assessment of therapeutic usefulness
  - There is no existing method of treatment, prophylaxis, or diagnosis.
  - Therapeutic usefulness with respect to existing treatment.
- Standpoint of efficacy
- Standpoint of safety
- Reduction of physical and mental burden on the patient[3]

Applicants are requested to submit results of clinical studies up to late Phase II as a rule as data for estimating the clinical usefulness. Hearings and inquiries are undertaken for the applicant as required and the designation is decided after hearing opinions of experts in the field. The results, including reasons, are notified to the applicant in writing. Orphan drugs are all handled as products for priority interview advice and an application is not required[3].

- **Sakigake (Forerunner) Review and Designation System:**
  In 2014, the Japanese Ministry of Health, Labor, and Welfare introduced the Sakigake (Forerunner) Review and Designation System (Refer Table 2), 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[10].

  Sponsors seeking Sakigake Designation must abide by different rules than they do when they seek BTD 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[10]. The designation of Keytruda as Sakigake for the unrespectable, 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 dataand would be subject to ongoing clinical studies and safety surveillance while on the market.

  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. Once qualified, PMDA commits to reviewing the application within nine months, rather than the standard twelve months. In 2015, PMDA and MHLW instituted the Sakigake Designation System, which is similar in key respects to BTD[10].

  It has designated six development drugs to date – five by Japanese sponsors, and one by a multinational sponsor (Merck's Keytruda [pembrolizumab] for unresectable, advanced, or recurrent gastric cancer).

  PROCEDURE:

  - **Initiation by applicant**: Applicant has to submit the application to Evaluation and Licensing Division (ELD) and to be reviewed at PMDA
  - **Initiation by ELD**: ELD has to approach a potential candidate and the outcome has to be notified within 30 days after the submission, upon agreement by the applicant[10]

  To qualify, a therapy must meet four criteria:

  - It targets a serious or life-threatening condition
  - It demonstrates improvement over existing therapies in terms of safety or efficacy,
  - It has a different mechanism of action than existing therapies, and
  - The sponsor intends to conduct early clinical development and submit the drug for initial regulatory approval in Japan[3]

  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.

  Advantages of Sakigake:

  - Decreased clinical consultation time from the submission of materials from 2 months to 1 month
  - Pre- application consultation
  - Prioritized review from originally being 12 months to now being 6 months.
  - Review partner (PMDA Manager as a concierge)
  - Extension of the post marketing safety measures i.e. Re-examination period

Benefits of SAKIGAKE Designation:

- Lead time for PMDA Formal Consultations shortened to 1 month (standard lead time for application is 2-3 months prior to consultation)
- Prioritized NDA review
  - Ability to submit English materials for pre-review
  - NDA Review period shortened to 6-months
  - Ability to submit Phase 3 study results following NDA submission
- PMDA Review "Concierge"- Assignment of a PMDA manager to oversee the entire approval process, including issues related to conformity assurance, quality management, safety measures, review, etc
- Post-Marketing re-examination period extended up to 10 years
- Premium pricing increase of 10-20%

Conditions for SAKIGAKE Designation:

- The drug possesses a new and different mechanism of action from already approved drugs

- The drug treats either:
  - A serious life-threatening disease
  - A chronic disease which deteriorates patients' QOL and for which there is currently no viable treatment
- The drug is expected to be more effective than currently approved treatments
- First approval targeted for Japan, and either (both preferable) of the following:
  - First in Human (FIH) Study conducted in Japan
  - Proof of Concept (POC) Study conducted in Japan

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**[10]**.**

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**.

- **Orphan Drug Designation**

Method:

We have compared the Orphan Drug Designation program in the US and Japan, which are under the agency of US (FDA) and the other being under the agency of Japan (MHLW). All regulation documents related to expedited approval were obtained from websites of the respective authorities: the FDA (US Food and Drug Administration) and the Pharmaceuticals and Medical Devices Agency (PMDA). Prerequisites needed for collection of the post-marketing clinical data were identified from the guidance documents. The pathways and the programs were later categorized based on the requirement of pre/post- marketing data requirements, evaluation of the post-marketing data[11,12].

As defined under section 526 of the Federal Food, Drug and Cosmetics Act (the Act), the term ***Rare Disease or Condition*** means any disease or condition which

- Affects less than 200,000 persons in the United States, or
- Affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug.

Orphan product means a drug/biologic intended for use in a rare disease or condition as defined in section 526 of the Act.

Designation:

- The Orphan Drug Act (ODA) provides for granting special status to a drug or biological product ("drug") to treat a rare disease or condition upon request of a sponsor. This status is referred to as orphan designation (or sometimes "orphan status")
- For a drug to qualify for orphan designation both the drug and the disease or condition must meet certain criteria specified in the ODA and FDA's implementing regulations in 21 CFR Part 316
- A sponsor seeking orphan designation for a drug must submit a request for designation to OOPD with the information required in 21 CFR 316.20 and 316.21
- Usually Replaces IND Application as IND is not mandatory for orphan products
- Does not alter the standard regulatory requirement and marketing approval process (Safety and effectiveness of a drug must be established through adequate and well-controlled studies)
- Under 21 CFR 316.23
- A sponsor may request orphan drug designation at any time in its drug development process prior to the time that sponsor submits a marketing application for the drug for the same rare disease or condition and
- A sponsor may request orphan drug designation of an already approved drug for an unapproved use without regard to whether the prior marketing approval was for a rare disease or condition
- OOPD may request more information, Refuse the designation or Grant the Orphan Drug Designation[11]

Table-1: Expedited Approval Pathways and Programs in the USA[5,6,8]

Programs	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review	Expanded Access
Regulatory Pathway(Authority, Year of issue)	FDA,1998	FDA,2012	FDA,1992	FDA,1992	FDA,2015
Nature of the program	Designation	Designation	Approval Pathway	Designation	Designation
When to submit request	-With IND or after -But no later than the pre-BLA or pre-NDA meeting	-With IND or after -But no later than end-of-phase 2 meeting	-Submit during drug development	With original NDA,BLA or efficacy supplement	-Submit prior to commencement of an IDE pivotal study
Timeline for authority response	Within 60 calendar days of the receipt of the request	Within 60 calendar days o the receipt of th request	Not specified	Within 60 calendar days of the receipt of the original BLD,NDA or efficacy supplement	Meeting will be held within 75-90 days of request with pre submission by the sponsor
Qualifying criteria	-A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR -A drug that has been designated as a qualified infectious disease product	-A drug that is intended to treat serious conditio AND prelimina clinical evidenc indicates that th drug may demonstrate substantial improvement or clinically significant endpoint(s) ove available therapies	-A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	-An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR - Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505Ab OR -An application for a drug that has been designnated as a qualified infect-ious disease product OR -Any application or supplement for a drug subm-itted with a priority review voucher	-A device intended to treat or diagnose or life-threatening or irreversibly debilitating disease or condition AND addresses an unmet need

Features	-Action to expedite development and review; -Rolling review	-Intensive guidance efficientdrug development; -Organizational commitment; -Rolling Review	-Approval based effect on a surroga endpoint or intermediate clini endpoint that reasonably likely predict a drug's clini benefit	-Shorter review time of marke-ting application (6 months com-pared to 10 month for the standard review)	-Reduced premarket data

Table-2: Expedited Approval Pathways and Programs in JAPAN[3,10]

Programs	**Fast Track**	**SAKIGAKE**	**Conditional & Time Limited Approval**	**Priority Review**	**Expanded Access**
Regulatory Pathway(Authority, Year of issue)	_	MHLW,2015	MHLW	MHLW	_
Nature of the program	_	Designation	Pathway	Designation	_
Timeline for authority response	_	To be notified within 60 days of the application.	_	_	_
Qualifying criteria	_	-It targets a serious or life threatening condition, -It demonstrates improvement over existing therapies in terms of safety or efficacy, -It has a different mechanism of action than existing therapies, and -The sponsor intends to conduct early clinical development and submit the drug for initial regulatory approval in Japan.	-The sponsormust confirm the safety and effectiveness of the therapy through post-market studies.	-A Drug must target a serious or life-threatening condition -It must exhibit improved clinical usefulness over existing therapies in terms of safety, efficacy, or patient quality of life.	_
Features	_	-Rolling Review (SAKIGAKE Comprehensive Consultation); - 6-month review period; -Designation required	- Get a conditional approval before being reviewed -Requires post marketing data	-9-month review period; - Designation required	_

Table-3: Classifying the Expedited Programs[8]:

Sr. No	Types of Pathways	Agency	Requirement of clinical data	
			Pre-marketing Data	Post-marketing Data
1.	Priority Review (Expedited Approval)	FDA (USA)	Comprehensive data are required	Not Required
2.	Fast Track (Expedited Approval)		Comprehensive data are required	Not Required
3.	Accelerated Approval (Conditional Approval)		Comprehensive data are not required Early, surrogate or intermediate endpoints are accepted	Required
4.	Breakthrough Designation (Development Support)		Comprehensive data are required	Not Required
5.	Sakigake	PMDA (JAPAN)	Comprehensive data are required	Required
6.	Priority Review		Comprehensive data are required	Required
7.	Conditional & Time Limited Approval		Comprehensive data are not required Early, surrogate or intermediate endpoints are accepted	Required

Table-4: Key contents required for Orphan Drug Designation[11,12]:

USA	JAPAN
• Application form and • Sponsor statement • Name and address of sponsor • Description of rare disease or condition with indication • Discussion of scientific rationale including all supportive data • Description of clinical superiority, if relevant Justification of a valid subset, • Summary of regulatory and development history • Documentation of prevalence of < 200,000 in the USA or evidence that there is no reasonable expectation that the costs of research and development can be recovered by the sales • Sponsor statement of party of interest	• Application form and • Data on the number of patients with objective statistical data for whom the drug will be indicated • Data on medical needs • Data on the disease including etiology and symptoms • Data on the current status such as availability of similar drug and treatment • Data on the theoretical rationale for the use of the drugs • Related data in a draft dossier of application for marketing authorization, which is available at the time of application for orphan drug • Development plan (data on the possibility of development), including outline of the development plan, current development status, expected test items, duration of the study and necessary expenses • Preparation of summary of the orphan drug.

Table-5: Features of Orphan Drug Designation[11,12]:

Features	USA	Japan
Drug legislation	ODA	Article 77-2 of the Pharmaceutical Affairs Law
Medicinal Products	Yes	Yes
Key Designation Criteria	Affects less than 200,000 persons in the USA Or Affects more than 200,000 in the USA and for which there is no reasonable expectation that the cost of developing and making a drug for such disease or condition will be recovered from sales in the USA	The number of patients who may use the drug should be less than 50,000 in Japan The drug should be indicated for the treatment of a serious disease, with high unmet medical need (no appropriate alternative treatment or expected higher efficacy or safety) Theoretical rationale for the use of the product for the target disease, and appropriate development plan.
Review period	Review cycle typically 90 days	None specified
Bodies involved in designation procedure	FDA OOPD	MHLW PAFSC PMDA
Public Information	OOPD webpage	Government Gazette
Procedure	Fast Track Procedure	Priority Review
Market Exclusivity	7 years	Extension of the re-examination period to up to 10 years
Incentives	Fees Reduction Tax CreditsMarket Exclusivity Higher rate for regulatory approvals Pediatric studies can be waived Shorter time to market R&D grants Premium pricing Favorable reimbursement Protocol Assistance Grant Program	Fees Reduction Preferential tax treatment Subsidy payment Guidance and Consultation Priority review Extension of reexamination period

An example of a drug with both orphan and non-orphan indications is **Humira (adalimumab)**. Since its initial approval in 2002 for rheumatoid arthritis, Humira has received approval for several new indications, including four under the Orphan Drug Act.

Incentives in the USA:

- **7 years** of market exclusivity in the U.S
- Waived payment of regulatory fees – a boon for smaller (less than 250 staff) U.S. developers
- Grants for development
- Additional meetings with the FDA
- The waiver of the requirement for a pediatric plan
- Waived fees for New Drug Applications (NDAs), and Biologic License Applications (BLAs)[11]

In the U.S., the condition must be rare, and the reason for treatment must be explained – a somewhat more relaxed standard. The FDA requires only a rationale for the orphan status of the drug, not necessarily the supporting data.

Criteria for Orphan Drug Designation in Japan:

1. Number of patients:
   The number of patients who may use the drug should be less than 50,000 in Japan*
   *less than 3.9 per 10,000 individuals approximately.

2. Medical needs:
   The drugs should be indicated for the treatment of serious diseases, including difficult to treat diseases. In addition, they must be drugs for which there are high medical needs satisfying one of the following criteria. There is no appropriate alternative drug or treatment in Japan.

   High efficacy or safety is expected compared with existing medical products in Japan.

3. Possibility of development:

There should be a theoretical rationale for the use of the product for the target disease, and the development plan
should be appropriate MHLW holds jurisdiction over the Pharmaceutical Affairs Law and the MHLW makes orphan designation decisions on a case-by-case basis. The decision is based on the opinion of the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), who review a scientific report prepared by the Pharmaceuticals and Medical Devices Agency (PMDA). As with other regulatory submissions, Japanese data are considered to be of most value and the application for orphan designation must be in Japanese.

Role of MHLW, PMDA, and NIBIO in Orphan Drug Designation[12]:

MHLW:

- Designation and approval of orphan drugs
- Pre-designation consultation for orphan drugs
- Payment for the operational cost of NIBIO
- Policy making related to designation and approval of orphan drugs
- Measures against intractable diseases, such as promotion of research and reduction of co□payment of medical fees

PMDA:

- Support MHLW's conclusion for orphan designations by providing prior assessment reports
- Priority scientific consultation for marketing authorization
- Priority review of orphan drugs

NIBIO:

- Subsidy payment to the applicant
- Accreditation for research expenses to be used by the applicant
- Provision of guidance and consultation to the applicant

Key contents to be given in the application form:

- Description of the target disease:
  - ✓ Summary of the cause and symptom
  - ✓ Number of patients (prevalence of the condition)
  - ✓ Justification as to why existing methods are not satisfactory
- Medical Plausibility:
  - ✓ Mechanism of action
  - ✓ Clinical data
- Summary of current regulatory or development status, and marketing history, out of Japan
- Summary of current development status and plan of the product in Japan

Incentives in Japan:

- Grant in Aid for R&D Expenses:
  - Applicants can receive subsides through NIBIO (In FY2012, 21 items received grants totaling 880 million yen*.) *Appropriately 8.98 million USD
- Administrative and Scientific Advices:
  - Pre-submission meeting/advices by MHLW on application for orphan drug designation (free of charge)
  - Administrative advices by NIBIO on R&D after the designation (free of charge)
  - Priority Consultation by PMDA(lower rate than normal drugs)
- Authorization of R&D Expenses for Tax Deduction:
  - 12 percent of total R&D expenses for orphan drug during the grant period is deductible
  - NIBIO authorizes the R&D expenses for tax deduction
- Priority Consultation and Priority Review
  - Priority review for marketing authorization
    Lower user fees are applicable for review and scientific consultation
- Extension of re-examination period:
  - The re-examination period for the drugs will be extended up to 10 years for drugs (Usually 8 years for NDA)
  - Re-examination period acts as data exclusivity period[12]

Process of Orphan Designation:

1. Application of pre-submission meeting by the sponsor to MHLW
2. Pre-submission meeting between MHLW and the sponsor
3. Submission of the application by sponsor to MHLW
4. Validation of the application by MHLW
5. MHLW sends the application for review to PMDA
6. PMDA reviews and evaluates the application
7. PMDA sends a review report to MHLW
8. MHLW refers the application to PASFC
9. A discussion panel is held at PASFC for the application
10. PAFSC sends its recommendation to MHLW
11. Administrative work is completed at MHLW
12. MHLW sends a notification to the sponsor and simultaneously to the gazette government and the general public (for public assessment report)
13. Sponsor sends the post designation incentives request to NIBIO and PMDA
14. MHLW PMDA MHLW: Ministry of Health, Labor, and Welfare PMDA: Pharmaceuticals and Medical Devices Agency NIBIO: National Institute of Biomedical Innovation[12]

Examples of Orphan Designated Drug in Japan:

- ➢ Galsulfase – Mucopolysaccharidosis VI (Clinical research of 3 cases)
- ➢ Dasatinib – CML/ALL (Clinical Trial of 41 CML cases & 13 ALL cases)
- ➢ Rufinamide - Lennox-Gastaut syndrome (Clinical Trial of 59 cases & Placebo controlled trial)

Challenges:

- Pharmacovigilance
- Small clinical trials
- Modeling and simulation
- Off-label use
- Ultra-orphan drugs
- Bio-marker
- Global clinical trials
- Surrogate end-point

- Manufacturing
- Dose finding
- Registry
- Translational research

CONCLUSION:

Patients suffering from rare conditions are entitled to the same quality of treatment as patients with common diseases. Orphan legislation offers important incentives to encourage the development of medicinal products for rare diseases and the success of the legislation has been demonstrated. Although similarities exist in the designation procedures in the EU, USA, and Japan, there are differences in the key criteria used to determine whether a medicinal product can be considered an 'orphan drug'. These include the definitions of the orphan condition to be treated and the prevalence criteria. Despite these differences, numerous medicinal products designated as orphan have subsequently achieved marketing authorization, highlighting the success of the incentive systems in encouraging the development of treatments for rare diseases

Comparing the Expedited Programs and the Pathways in the USA with the Conditional and Time-Limited Approval of medicinal products in Japan.

Qualifying Criteria:

- Should treat a serious or life-threatening target disease
- Should treat a limited target disease patient population
- Treats a disease lacking the medical treatment options
- Is superior to the existing medical treatment options

All the Expedited Programs or Pathways of the US address the unmet medical needs. More than half of the pathways are intended for treating serious or life-threatening diseases. Few pathways namely, the Expanded Access and the Fast Track are the ones which fall under the category of having no alternatives treatment options, while the Priority Review, Breakthrough Therapy and Accelerated Approval lies under the category for being superior to the existing treatment.

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