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COMPARATIVE REGULATORY FRAMEWORKS FOR REPURPOSED DRUGS: A STUDY OF USFDA AND PMDA REQUIREMENTS

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ABSTRACT

Drug repurposing is a promising strategy for developing new therapeutic options by leveraging existing compounds. However, regulatory pathways for repurposing vary across regions, posing challenges for global pharmaceutical manufacturers. This study compares the regulatory frameworks for repurposed drugs in the US and Japan, two key markets with distinct approaches. The FDA of US and PMDA of Japan establish guidelines, requirements, and approval processes, identifying similarities and differences. This research also investigates the implications of these regulatory disparities for Indian pharmaceutical manufacturers, who seek to capitalize on opportunities presented by drug repurposing to address unmet medical needs and enhance their competitive position in the international market. By assessing comparative regulatory analysis and industry perspectives, this study aims to provide valuable recommendations for Indian pharmaceutical manufacturers to navigate regulatory complexities effectively, streamline drug repurposing processes, and enhance their competitiveness in the global pharmaceutical landscape.

Keywords: Drug repurposing, US FDA, PMDA, Regulatory frameworks, 505(b)(2)

INTRODUCTION

Drug repurposing, or drug re-profiling, is a strategy used by researchers to repurpose existing drugs for new therapeutic uses in various diseases, especially when

traditional de novo development is not cost-effective or a cure is urgently needed, such as in COVID-19 treatments **[1, 2]**.

United States Food and Drug Administration

The US FDA (Food and Drug Administration) recognizes the potential of drug repurposing, which is a strategy to find new uses for existing drugs **[3, 4]**. This approach has gained attention after the FDA granted emergency use authorization for several repurposed drugs to treat Covid-19. The FDA has seen success stories in drug repurposing. For example, during the Covid-19 pandemic, certain repurposed drugs received emergency use authorization **[3]**. FDA sees value in drug repurposing as it can potentially lead to quicker development and approval of treatments for various diseases and conditions **[4]**. However, there are still challenges to overcome, and more research is needed to fully realize the potential of this approach **[3]**.

Pharmaceuticals and Medical Device Agency

The Pharmaceuticals and Medical Devices Agency (PMDA) of Japan appears to view repurposed drugs, also known as drug repurposing, as a potentially valuable approach for bringing new treatment options to patients faster and potentially at a lower cost. PMDA likely views repurposed drugs positively as a potential path for efficient development of new treatment options, but they would still require a rigorous scientific basis for approval.

USFDA guidance on Repurposed Drugs

In the US, there are three separate regulatory approval pathways that allow for the registration of distinct classifications of drugs, as outlined in the Food, Drug and Cosmetics Act, although only one of these (i.e., “505(b)(2)”), is relevant to drug repurposing. All drug candidates for repurposing must be submitted through Section 505(b)(2), regardless of whether it is for cancer therapeutics or alternate diseases **[5]**. A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted". An application for a not previously approved indication for a listed drug is eligible to submit 505 (b)(2) **[6]**. To achieve the 505(b)(2) approval, drug developers must identify a unique administration route or disease indication for their repurposed drug compared with the primary route and indication. Section 505(b)(2) applications must include patent certifications described at 21 CFR 314.50(i) and must provide notice of certain patent certifications to the NDA holder and patent owner under 21 CFR 314.52 **[7]**.

Comparison of 505 (b)(1) [NDA] with 505(b)(2) application: Although the two types of applications must meet the same standards for approval, but they differ in Source of information to support safety and effectiveness, patent certification requirements, BA/BE evidence, Exclusivity bars, and Processing within the FDA **[8]**.

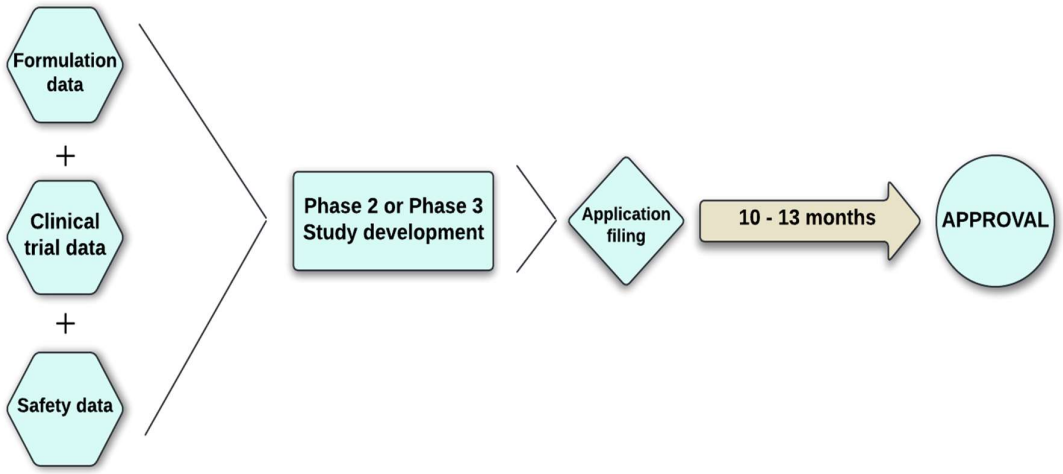

Figure 1: Regulatory filing pathway for repurposed drugs in USFDA

PMDA guidance on Repurposed Drugs

In Japan, the approval of repurposed drugs follows the guidelines stipulated in the "Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices" (Law No. 145, 1960) after revision according to the Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, 2013). The provisions of Article 14 of the "Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices" stipulate that, when a person with an intention to manufacture and market a drug has filed an application for approval of the manufacture and marketing of the drug, designated reviews should be conducted for the drug to be applied regarding the components/contents, dosage and administration, and indications of, and adverse reactions, etc., and the Minister of Health, Labour and Welfare shall give an approval for each product. When an application for approval is filed, evidence sufficient for proving the quality, efficacy, and safety of the application-related drug need to be presented using the documents with ethical and scientific validity and reliability on the basis of the medical and pharmaceutical academic standards at that time point **[9]**.

Approaches to drug repurposing

1. **Drug-Centric Approach**: This approach expands the application of an existing drug to a new indication. Examples include: Discovering off-label use of an approved drug for a new

patient population or medical condition beyond its existing license or patent, Identifying new uses for drugs withdrawn from circulation due to safety or post-market issues but still efficacious for other medicinal purposes and Repositioning drugs that have reached the end of their patent exclusivity period and now have generic competitors for new conditions.

2. **Disease-Centric Approach**: This approach matches diseases with no treatments or partially effective treatments with approved or failed compounds that have therapeutic impact. It is particularly valuable for rare diseases. For instance, a drug developed to treat cancer might also be effective for other diseases involving uncontrolled cell growth, such as psoriasis.
3. **Target-Centric Approach**: In this approach, a new indication without a treatment is matched with an established drug and its known target. The old and new indications typically differ significantly, but the drug's mechanism of action remains relevant **[2]**.

Classification of repurposed drugs

1) Therapeutic assets (of any modality) with remaining patent life but never approved for human use;

2) Therapeutics with remaining patent life that are currently approved for one or more indication(s) but have potential use in others;

3) Therapeutic assets with no patent life that are not currently marketed because they were either never approved or were withdrawn;

4) Therapeutics with no patent life currently manufactured by generic companies, approved for certain indications, and available by prescription from healthcare providers **[10]**.

Benefits of Drug Repurposing

- Repurposing medicines involves more advantages like lower development costs, shorter timelines, and economic and societal benefits for sustainable healthcare systems in the long term **[9, 10]**.
- New treatments for rare diseases: Repurposing offers a viable alternative to new drug discovery for rare diseases when candidates that have proven safe in either preclinical models or clinical human usage also show efficacy for a rare disease.
- Rapid response to emerging needs: Drug repurposing is beneficial during health emergencies to quickly identify potential treatments. During the COVID-19 pandemic, several drugs were repurposed under emergency authorization, including Remdesivir **[5]**, an antiviral developed as a treatment for Ebola and Dexamethasone **[6]**, a widely used steroid that reduces mortality in hospitalized patients requiring ventilation.
- Less or no animal testing required: When repurposing drugs, the

pharmacokinetics and pharmacodynamics insights are already known, so animal testing carried out in preclinical phases is eliminated **[2]**.

Barriers in repurposing:

- Barriers to Obtaining Marketing Authorisation: Obtaining marketing authorisation is an important hurdle for academic researchers, as the regulatory process is complex. While academic researchers have knowledge on how to perform high-quality clinical trials, they often lack detailed knowledge of the authorisation process, time and other resources to obtain regulatory approval **[11]**.
- Drug repurposing and intellectual property rights: Patent protections and IP are crucial for pharmaceutical organizations to secure new patent applications or licensing agreements for repurposed drugs. Ensuring commercial viability and access to the latest information on existing IP and patent protections are essential for successful patent expansion and licensing agreements. Timing is crucial to avoid losing exclusivity and extending patents **[2]**.

METHODOLOGY

A comprehensive analysis was conducted on the regulatory approval of repurposed drugs in the United States and Japan from 2014 to 2023, utilizing data collected from the official websites of the US Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA). This involved compiling information on approved repurposed drugs, including indications, regulatory pathways, clinical trial data, and approval dates. Comparative analysis was undertaken to discern trends and patterns in regulatory approval between the FDA and PMDA, evaluating similarities and differences in approval timelines and requirements. Regulatory guidelines and frameworks were retrieved and analyzed to identify key considerations such as safety, efficacy, pharmacovigilance, and labelling requirements for repurposed drugs in both countries. Subsequently, a harmonized guidance document was developed based on the comparative analysis, aiming to streamline regulatory pathways, foster collaboration between regulatory agencies, and facilitate efficient approval processes for repurposed drugs, tailored to address the unique regulatory landscape of both the US and Japan.

RESULTS AND DISCUSSION

The analysis of the USFDA's approach to repurposed drug approvals over a span of ten years (2014-2023) revealed a noteworthy surge in approvals, particularly in the year 2020. This marked increase can be attributed to the heightened approval of repurposed

drugs intended for the treatment of COVID-19 **[12] (Figure 2)**.

The examination of the repurposed drugs approach by the PMDA involved analysing the number of approvals issued during the study period (2014-2023). The findings revealed that the PMDA has granted a higher number of approvals for repurposed drugs compared to the USFDA. Notably, in 2022, a record-high of 81 approvals were granted, indicating a significant endorsement of repurposed drug utilization by the PMDA **[13] (Figure 3)**.

A comparative analysis was conducted between repurposed drugs approved by the USFDA and the PMDA, revealing a discernible difference in approval patterns. The findings indicate that the PMDA exhibits a greater level of concern and emphasis on repurposed drugs in terms of approvals compared to the USFDA **(Figure 4)**.

Upon categorizing USFDA-approved repurposed drugs, a notable trend emerged: the majority of these drugs belong to the antineoplastics category. This finding underscores a significant focus on repurposing within oncology, reflecting efforts to innovate in cancer treatment. The prevalence of repurposed antineoplastics highlights the potential for leveraging existing drugs to address unmet needs in oncology. Such insights illuminate the strategic direction of drug development and therapeutic innovation in the fight against cancer **(Figure 5)**.

Categorization of PMDA-approved repurposed drugs revealed that a majority are related to anticancer therapies. This trend underscores a significant focus on repurposing within the oncology field by the PMDA. The prevalence of repurposed anticancer drugs highlights efforts to address critical needs in cancer treatment through innovative approaches. Such findings shed light on the strategic direction of drug repurposing and therapeutic advancements in oncology by the PMDA **(Figure 6)**.

This comparison highlights the key differences between the development and approval processes for new drugs and repurposed drugs, emphasizing the distinct approaches to research, preclinical studies, clinical trials, review processes, decision criteria, and post-market surveillance. While both processes prioritize safety and efficacy, repurposed drugs leverage existing knowledge to streamline development and approval **(Table 1, 2)**.

The **Table 3** contrasts approval timelines for NDAs and repurposed drugs in the US and Japan. While NDAs typically take several years, repurposed drug timelines may be shorter due to leveraging existing data. Both countries offer expedited review pathways for faster approval. Overall, repurposed drugs often have a significantly reduced timeline compared to NDAs. This highlights

the potential for accelerated access to treatments through drug repurposing strategies.

The listed studies or data can be referred to from the original submission when applying for repurposed drugs, following the ICH CTD format, which is applicable to both Japan and the US **(Table 4)**.

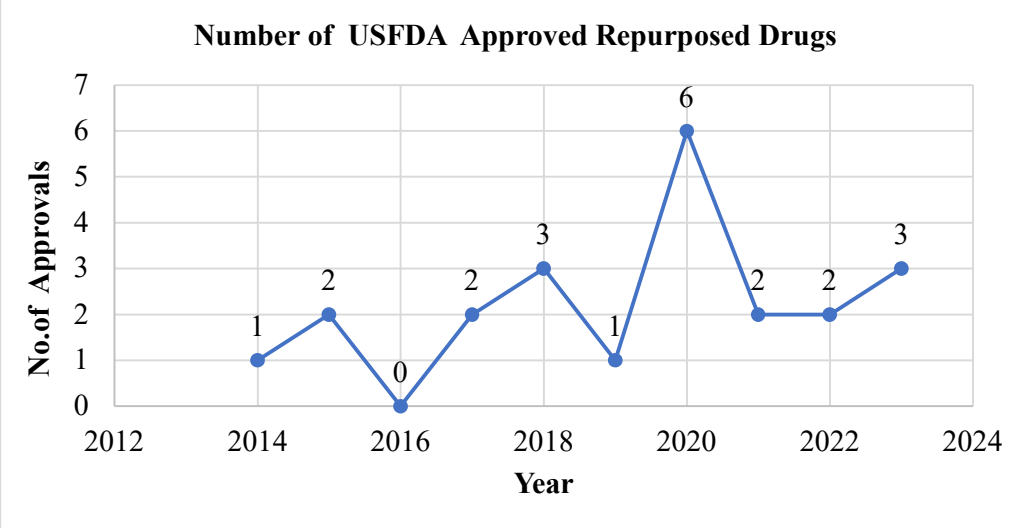

Figure 2: USFDA Approved Repurposed Drugs

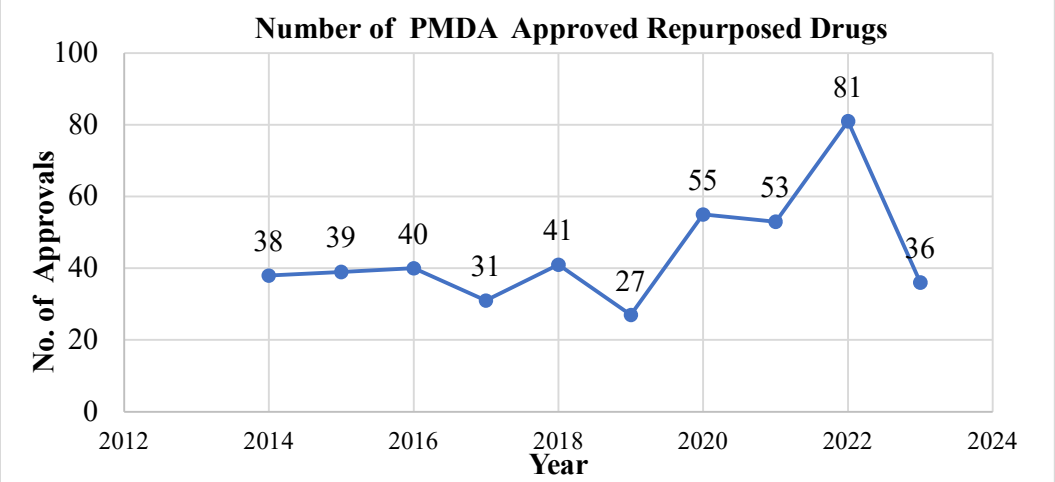

Figure 3: PMDA Approved Repurposed Drugs

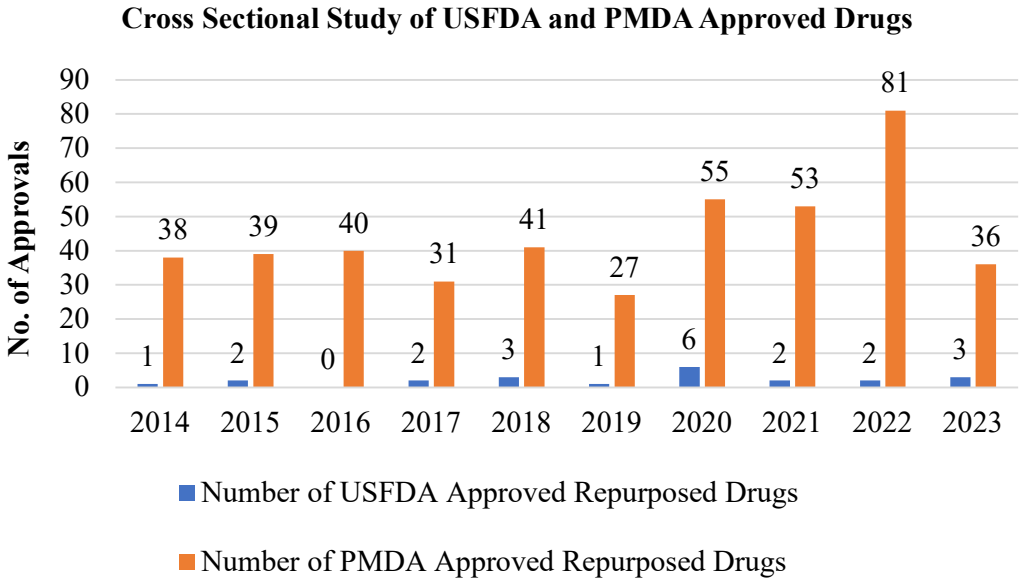

Figure 4: Comparative Analysis of USFDA & PMDA Approved Repurposed Drugs

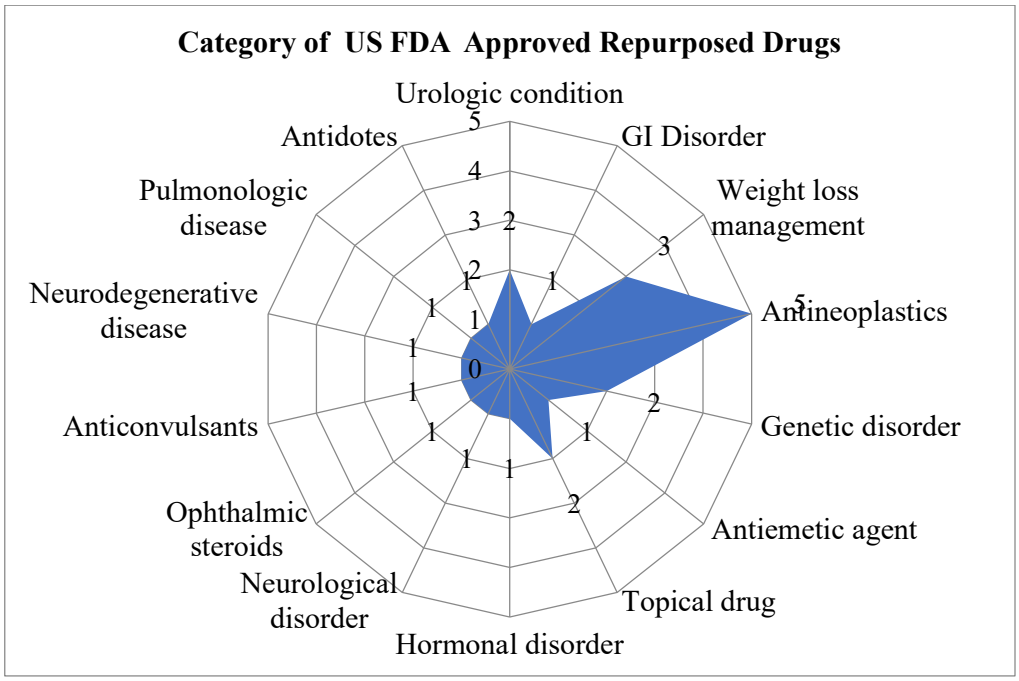

Figure 5: Category of USFDA Approved Repurposed Drugs from the year 2014 to 2023

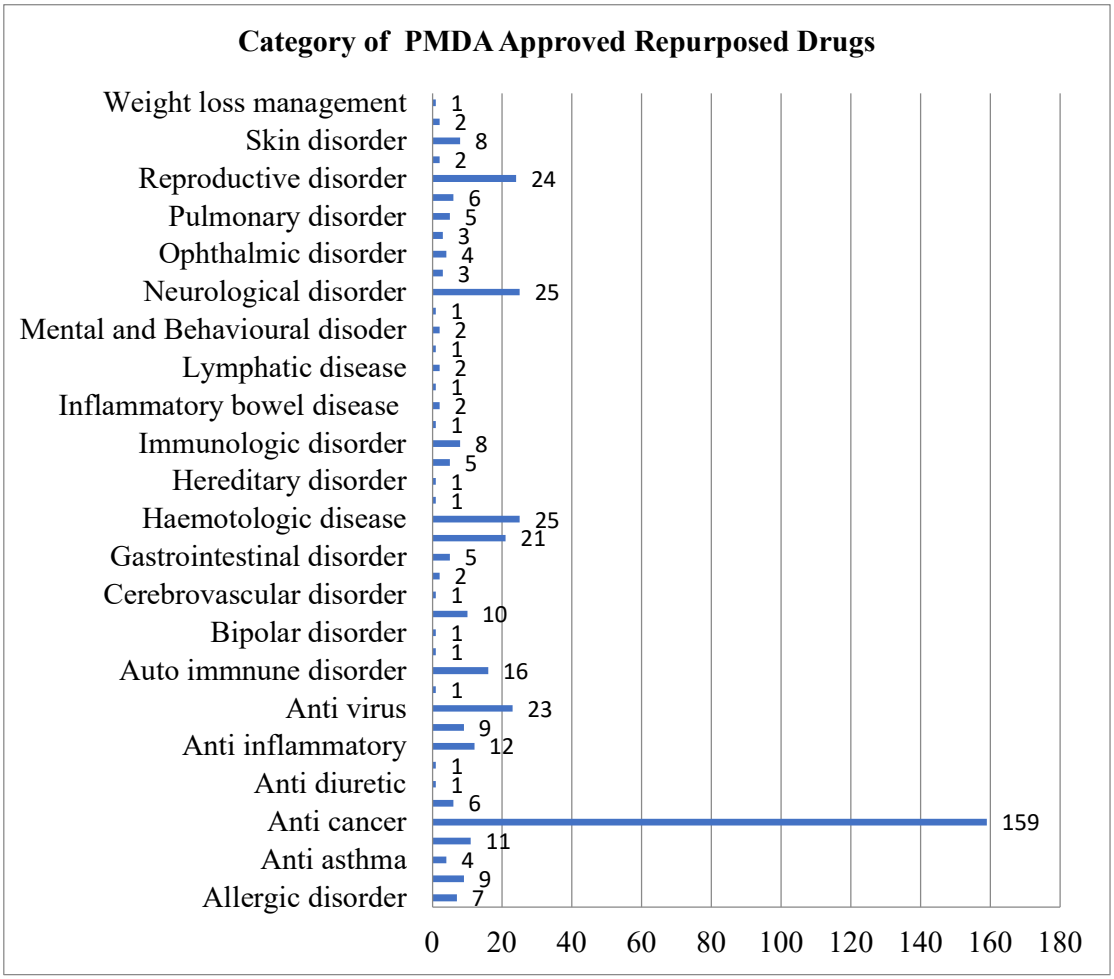

Figure 6: Category of PMDA Approved Repurposed Drugs from the year 2014 to 2023

Table 1: Comparison of development process of new drugs and repurposed drugs in US

Aspect	New Drugs	Repurposed Drugs
Regulatory Authority	**USFDA**	**USFDA**
Development Process	**Involves extensive research, discovery, and development from scratch**	**Utilizes existing drugs with known safety profiles and mechanisms of action**
Preclinical Studies	**Assess safety and efficacy in animal models**	**Focus on evaluating efficacy for new indications**
Clinical Trials	**Conducted in phases (I-III), focusing on safety and efficacy**	**May require clinical trials to demonstrate efficacy in new indications**
Review Process	**Rigorous evaluation emphasizing safety, efficacy, and quality**	**Comprehensive assessment focusing on safety, efficacy, and quality**
Review Timeframe	**Varies, typically several months to years depending on the complexity**	**Varies, typically several months to years depending on the complexity**
Advisory Committees/Expert Panels	**Utilizes advisory committees composed of independent experts**	**Employs expert panels consisting of knowledgeable professionals**
Decision Criteria	**Based on substantial evidence demonstrating safety and efficacy**	**Relies on scientific data, clinical trials, and evidence-based assessments**
Post-Market Surveillance	**Implements robust post-market surveillance programs**	**Conducts post-market monitoring and pharmacovigilance activities**

Table 2: Comparison of development process of new drug and repurposed drugs in JAPAN

Aspect	New Drugs	Repurposed Drugs
Regulatory Authority	PMDA	PMDA
Primary focus	Developing entirely new compounds with novel mechanisms of action.	Repurposing existing drugs for new therapeutic indications.
Preclinical Research	Extensive preclinical studies to evaluate safety and efficacy.	May leverage existing preclinical data and focus on specific indications
Clinical Trails	Phase I, II, and III trials to assess safety and efficacy.	Phase II/III trials for efficacy, often with shorter timelines.
Regulatory Approval Process	Follows a stringent regulatory pathway involving multiple phases.	Generally follows a similar pathway but may have expedited timelines.
Regulatory Review	In-depth review by regulatory agencies, such as PMDA.	Review may be accelerated if safety profile of the drug is well-known.
Market Entry Strategy	Often involves targeting niche markets or unmet medical needs.	Can target broader markets or expand indications for existing drugs.
Post-Market Surveillance	Rigorous monitoring for adverse effects and long-term safety.	Similar to new drugs but may leverage existing safety data.

Table 3: Timeline difference when compared to NDA and repurposed drug approval process in US and Japan

Stage	US (Standard)	US (Repurposed Drugs)	Japan (Standard)	Japan (Repurposed Drugs)
Pre-IND	3-6 months	1-3 months	3-6 months	1-2 months
IND submission	2-3 months	1-2 months	2-3 months	1-2 months
Clinical trials	2-5 years	1-3 years	2-5 years	1-4 years
NDA submission	12-18 months	6-12 months	12-18 months	6-12 months
Total timeline	5-8 years	4-6 years	5-8 years	4-7 years

Table 4: List of the studies or data can be referred from the original submission [14]

Module No	ICH CTD TITLE
1.13.3	Summary of safety information
2.5.5	Safety information
2.6.4	Pharmacokinetics
2.6.4.2	Methods of Analysis
2.6.4.7	Pharmacokinetic Drug Interactions
2.6.4.8	Other Pharmacokinetic Studies
2.6.6	Toxicology studies
2.7.4.5.4	Use in Pregnancy and Lactation
2.7.4.5.5	Overdose
2.7.4.5.7	Withdrawal and Rebound
2.7.4.6	Post-marketing Data
4.2.2.1	Analytical Methods and Validation Reports
4.2.3.8.1	Antigenicity
4.2.3.8.2	Immunotoxicity
4.2.3.8.3	Mechanistic studies
4.2.3.8.4	Dependence
4.3	Literature References

CONCLUSION:

Comparative study of US and Japanese regulatory perspectives on repurposed drugs underscores the importance of understanding regulatory nuances in different regions. The study highlights the prevalence of anti-cancer drugs among newly approved indications and suggests investing in repurposed drugs may offer a more efficient pathway to market approval. This study underscores the importance of understanding and navigating these regulatory landscapes for Indian pharmaceutical manufacturers seeking to enter the market with repurposed drugs. While the US and Japanese approaches

exhibit variations in their requirements and procedures, there are also areas of convergence that can serve as valuable points of reference for regulatory compliance. The implications of these regulatory frameworks extend beyond mere compliance to impact strategic decision-making, resource allocation, and market entry strategies for Indian pharmaceutical companies.

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