

Abstract

Background: To optimize and speed up the development for serious conditions, several expedited drug development pathways, approval programs and incentives such as orphan market exclusivity have been developed in the United States (US), the European Union (EU) and Japan. The overall aim is to speed up the development and approval process for products that address an unmet medical need and/or treat a serious or life-threatening condition. The idea is to give earlier marketing approvals and collect additional safety and efficacy data after the product is put on the market. The most significant benefit is the early access for patients.

Results: Data for novel/new drug approvals for 2019 show that in the US 60% (29/48) were designated in one or more expedited categories (Fast track, Breakthrough, Priority review, and/or Accelerated approval), 44% (21/48) were orphan drugs. In the EU 23% (15/66) were designated in one or more expedited categories (PRIME, Accelerated assessment, Conditional approval and/or Exceptional circumstances), 11% (7/66) were orphan drugs. In Japan 41% (26/ 64) were designated in one or more expedited categories (Priority review, Conditional early approval and/or Sakigake), 20% (13/64) were orphan drugs. In the US the absolute majority, i.e. 90% (19/21) of orphan drugs benefitted from one or more expedited category. In the EU 57% (4/7) of the approved orphan designated drugs used one or more expedited pathway. In Japan products that are granted orphan drug designation automatically also get Priority review, hence 100% (13/13) of the approved orphan designated drugs benefitted from at least one expedited pathway.

Conclusion: Which expedited category/(ies) to select is subject to careful consideration. For drug developers increased regulatory guidance can help build a crucial framework for the overall development plan and in determining the fastest and/or greatest value path to market. The goal being the expedited access to orphan drugs for patients globally.

Introduction

The expedited development categories are highly relevant for orphan drug developers. Taking advantage of early regulatory tools and designation programs, such as Fast-track, PRIME and/or Orphan drug designation is often reflected in increased stock prices/enterprise value and can, apart from accelerate the development, provide important signals to investors that the drug may have financial value. In the US, stacking of multiple expedited pathways is possible and is, in some therapeutic areas like oncology, a commonly seen phenomenon that's becoming the new norm.

The qualifying criteria and type of data needed for the expedited development categories can differ significantly between the regions (Table 1, 2 and 3), however studies indicate that for regulatory mechanisms with relative similarity, there is a significant disparity in the granting of designations in some therapeutic areas.

Table 1, Expedited Drug Development Programs in the US, the EU and Japan

Expedited Category	Description	Benefits
FDA Fast Track	Facilitate the development and expedite the review of drugs to treat serious conditions AND nonclinical or clinical data showing the potential to address unmet medical need OR a drug that has been designated as a qualified infectious disease product	-Frequent meetings with FDA to discuss the drug development plan -Frequent written communication from FDA on the program, such as the design of the proposed clinical trials, use of biomarkers etc. -Eligibility for Accelerated Approval and Priority Review (if relevant criteria are met) -Rolling Review (e.g. being able to submit completed sections of Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than having to wait until all sections of the application are available)
FDA Breakthrough (BTD)	Expedite the development and review of drugs which may demonstrate substantial improvement over available therapy	-All the benefits of Fast Track -Intensive guidance on an efficient drug development program -Organizational commitment with senior FDA managers
FDA Regenerative Medicines Advanced Therapy (RMAT)	Eligible for Regenerative medicines (and a combination thereof) that intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition	-All the benefits of Fast Track and BTD but does not (like BTD) require evidence that the product may offer a substantial benefit over existing therapies -Provides early opportunity to meet with the regulators
EMA PRIME	Enhanced support for the development of medicines that target an unmet medical need. Based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development and speed evaluation	-Guidance on the overall development plan and regulatory strategy and scientific advice at key development milestones, involving additional stakeholders such as HTAs -Potential for accelerated assessment at the time of an application for marketing authorization
PMDA Sakigake	Puts highly useful and effective drugs for treating serious diseases to practical use as early as possible	-All Priority review designation features -Prioritized clinical trial and pre-application consultation -Assigned PMDA manager -Post marketing safety measures

Table 2, Non-standard Marketing Authorization Approval Procedures in the US, the EU and Japan

Expedited Category	Description	Benefits
FDA Priority Review	Directs agency resources to the evaluation of drugs that represent significant improvements in safety or effectiveness compared to standard marketing approval applications	-Review time of marketing authorization application shortened from 10 months to 6 months
FDA Accelerated Approval	Allows drugs intended for serious conditions that fulfill an unmet medical need to be approved based on a surrogate endpoint	-Conditional approval granted with surrogate endpoint(s) from phase II or interim phase III trial data; confirmatory trials with hard clinical endpoints are required downstream of marketing approval
EMA Accelerated Assessment	Expedite the evaluation of products of major interest in terms of public health and innovation	-Review time shortened from 210 days to 150 days
EMA Conditional Approval	Allows drugs fulfilling an unmet medical need for severe, life threatening or rare (orphan) diseases to be approved with limited clinical safety or efficacy data, provided a positive benefit-risk balance can be shown	-Conditional approval granted before all data are available (valid for one year on a renewable basis, when pending studies are provided it can be converted to a standard marketing approval)
EMA Exceptional circumstances	Allows drugs fulfilling an unmet medical need for severe, life threatening or rare (orphan) diseases to be approved without comprehensive safety or efficacy data. Applied when a disease is so rare, or a clinical endpoint is so difficult to measure (for scientific or ethical reasons) that comprehensive safety and efficacy data are not expected to be obtained	-Conditional approval granted before all data are available (reviewed annually to reassess positive benefit-risk balance, not expected to ever be converted to a standard marketing approval)
PMDA Priority Review	Provides faster access to new therapies responding to high medical needs, includes products such as orphans and HIV medicines	-Review time shortened from nine to six months
PMDA Conditional Early Approval	Puts highly useful and effective drugs for treating serious diseases to practical use as early as possible Based on exploratory clinical data	-Early application through confirmation of a certain degree of efficacy and safety -Shortened overall review time for priority review

To encourage the development of orphan drugs several incentives are available for drug developers after the drug has obtained orphan drug designation. Drugs with orphan designation in the US are eligible for grants, a 50% tax credit for expenditures incurred during the clinical testing phase, and a seven-year marketing exclusivity period. In the EU sponsors benefit from reduced fees for protocol assistance (a type of scientific advice specific for designated orphan medicines), ten years market exclusivity once the medicine is on the market (can be reduced if the orphan criteria is no longer met) and fee reductions (available depending on the status of the sponsor and the type of service required). In Japan designated drugs can receive subsidies to reduce the financial burden of product development, tax credits, lower user fees, priority consultation, extension of the re-examination period up to 10 years etc.

Table 3, Criteria for Orphan Drug Designation in the US, the EU and Japan

The US	The EU	Japan
-Fewer than 200 000 people in the US affected -It is unlikely that marketing the medicine in the US would generate enough return to justify the investment needed for its development	-The drug should be intended to prevent, diagnose or treat a life threatening or chronically debilitating disease. -The condition may not affect more than 5 in 10 000 people or individuals. -Satisfactory methods of diagnosis, prevention or treatment do not exist/are not authorized or, if a medicine exists, the orphan drug being studied should demonstrate significant benefit over the existing one	-Fewer than 50 000 people in Japan are affected -High medical need, i.e. no appropriate alternative drug, medical device or treatment available or significant improvement of efficacy/safety expected over existing products -Appropriate theoretical rational and development plan

Methods

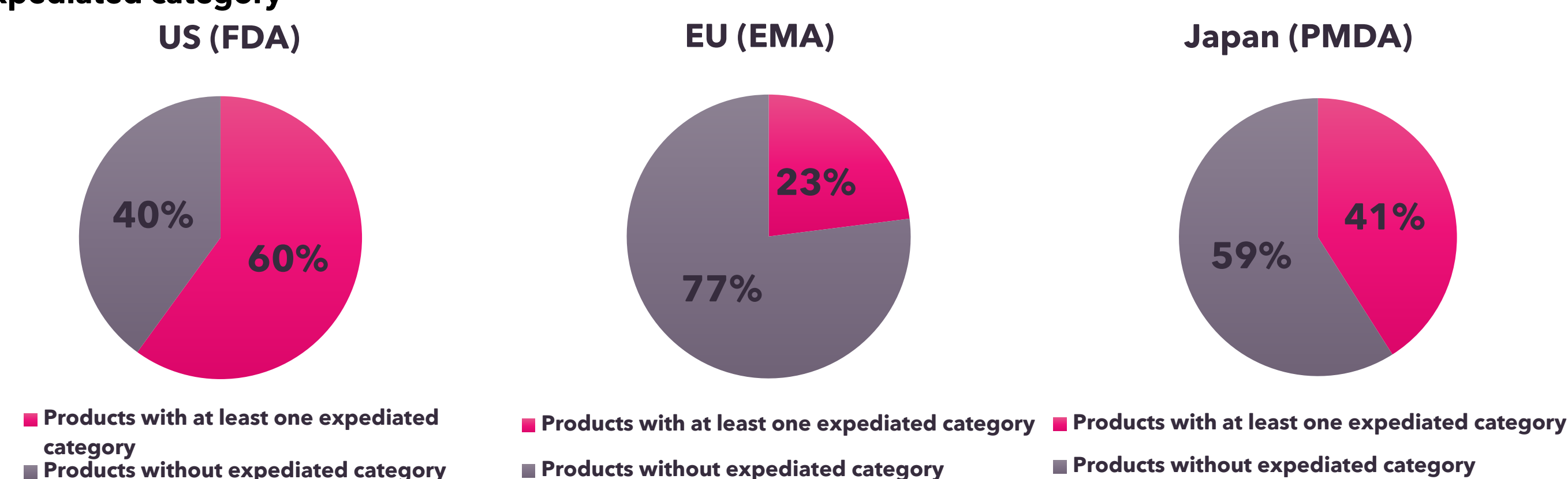
Data on novel/new drug approvals for 2019 was extracted from the webpages of the US FDA, the EU EMA and Japan PMDA. Some general inclusion and exclusion criteria was applied to create consistent indicators for New Active Substances (NAS), New Molecular entities (NME) and Biologics due to differences in classification and reporting styles in the US, the EU and Japan. New developments of previously authorized products, classified as having a significant technical or therapeutic innovation by the FDA, the EMA and/or the PMDA were included in the analysis. Only new developments of orphan designated products were included in the analysis. Combination products (combinations of previously authorized substances), generics, biosimilars and well-established use (literature-based) products were excluded.

Results and Discussion

Designation of Expedited Categories in the US, the EU and Japan 2019

The data for 2019 show that 60% (29/48) of the new/novel approvals in the US were designated in one or more expedited categories (Fast track, Breakthrough, Priority review, and/or Accelerated approval). In the EU 23% (15/66) were designated in one or more expedited categories (PRIME, Accelerated assessment, Conditional approval and/or Exceptional circumstances). In Japan 41% (26/ 64) were designated in one or more expedited categories (Priority review, Conditional early approval and/or Sakigake), Figure 1.

Figure 1, Proportion of New/Novel approvals by each Agency for 2019 that benefitted from at least one expedited category

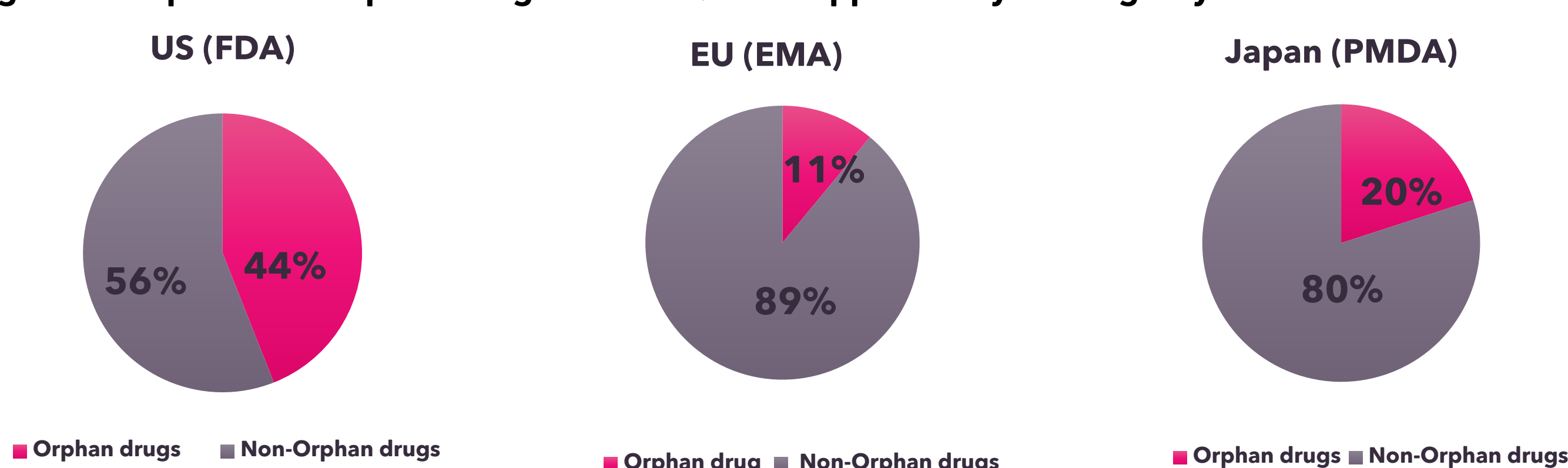


US (FDA): Fast track, Breakthrough, Priority review, and/or Accelerated approval; EU (EMA): PRIME, Accelerated assessment, Conditional approval and/or Exceptional circumstances; Japan (PMDA): Priority review, Conditional early approval and/or Sakigake

Approved Orphan Designated Drugs in the US, the EU and Japan 2019

In the US 56% (21/48) of the New/Novel approvals were orphan designated drugs, in the EU this number was 11% (7/66) and in Japan 20% (13/64) of the New/Novel approvals was issued for orphan designated drugs, Figure 2. In Japan, obtaining orphan designation also results in getting Priority review whereas orphan designations are not an expedited pathway *per se* in the EU or the US.

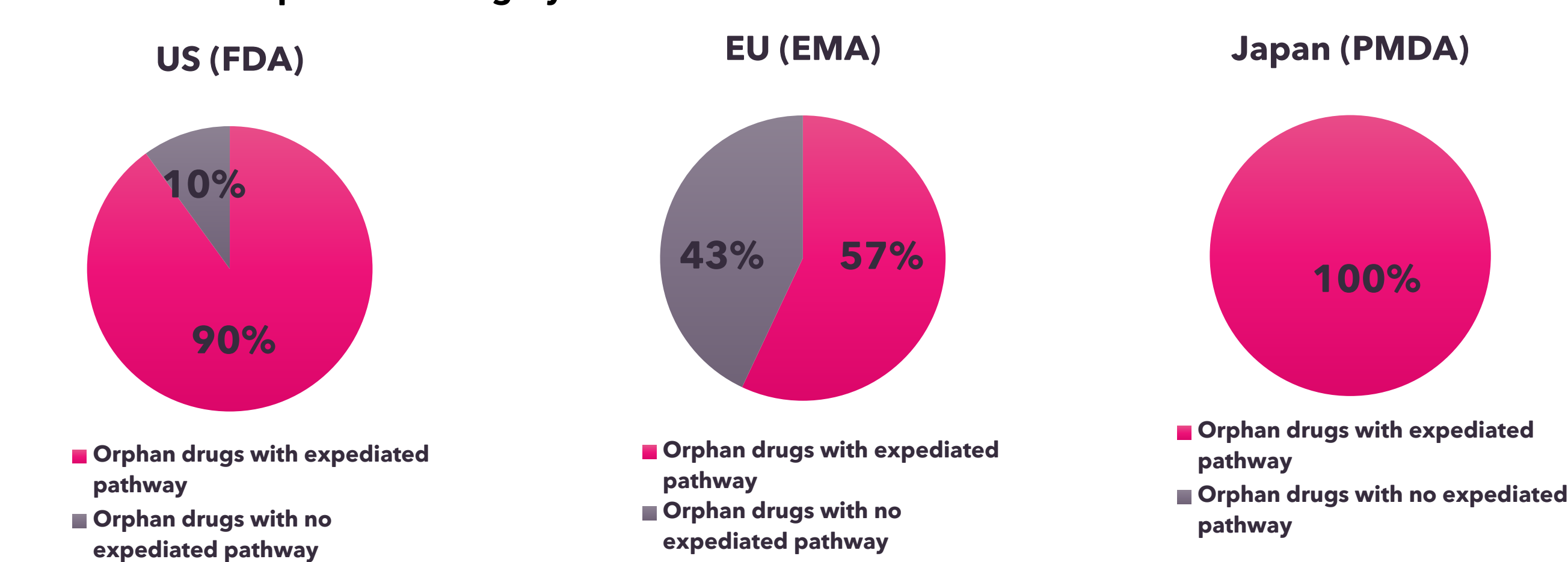
Figure 2: Proportion of Orphan designated New/Novel approvals by each Agency for 2019



Approved Orphan Designated Drugs in the US, the EU and Japan 2019 that benefitted from at least one expedited category

In the US the absolute majority, i.e. 90% (19/21) of the approved orphan drugs benefitted from one or more expedited category. In EU approximately little more than half, 57% (4/7), of the approved orphan drugs used one or more expedited pathway. In Japan, products that are granted orphan drug designation automatically also get priority review, hence 100% (13/13) of the approved orphan designated drugs benefitted from at least one expedited pathway, Figure 3.

Figure 3: Proportion of Orphan designated New/Novel approvals by each Agency for 2019 that benefitted from at least one expedited category



US (FDA): Fast track, Breakthrough, Priority review, and/or Accelerated approval; EU (EMA): PRIME, Accelerated assessment, Conditional approval and/or Exceptional circumstances; Japan (PMDA): Priority review, Conditional early approval and/or Sakigake

Drug developers without previous orphan drug development knowledge may conclude, in hindsight, that they should have adopted a different strategy, one that could have reduced the costs and time for their product to reach patients. Especially for small biotech companies, obtaining funding and justifying costs can be challenging, and strategic planning and regulatory knowledge early during product development is crucial. In the end, the expedited pathways option may mean that the regulatory approval is based on just one fundamental trial, or one surrogate endpoint. This makes it vital that the trial is appropriately designed and that the endpoint are acceptable to all the agencies from which they are seeking approval.

Conclusions

Overall, US, EU and Japan have implemented a combination of regulations and policies aiming to ease and speed up the development of orphan drugs. While these may enable the availability and access to orphan drugs, there are also critical differences between the regions in terms of range and types of regulations and policies implemented. The figures for 2019 new/novel orphan drug approvals shows that the absolute majority (90%) of the orphan drugs in the US and Japan (100%) used one or more expedited pathway whereas EU indicate lower numbers (57%). Increased understanding of these differences may aid in determining new approaches to further facilitate the expedited development and approval of orphan drugs.

Having a strong understanding of the available regulatory tools and means how to expedite the drug development process in the US, EU and Japan can be especially helpful when designing an efficient drug development program. Early regulatory support and guidance on which expedited pathway to select in the respective regions, the type of data needed to qualify and when to apply for it will boost the overall development plan if done right.