Pharmaceutical Medicine

Supplementary information to the article

The qualitative value of facilitated regulatory pathways in Europe, USA, and Japan: Benefits, barriers to utilization, and suggested solutions

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Supplementary information

SI 1: Questionnaire

1. **Does your company have experience with using the following FRPs? Please write an 'X' in all applicable boxes.**

	FDA Breakthrough Therapy designation	FDA Fast Track	EMA PRIME (Priority Medicines)	PMDA Sakigake designation
No experience				
Currently developing a medicine with the hope of obtaining the designation				
Submitted an application for the designation and received the designation				
Submitted an application for the designation and did not receive the designation				
Submitted an NDA which received the designation				
Received an approval for the NDA with the designation				
Other, please specify				

Please provide any additional comments below

Please answer questions 2-6 for those FRPs where you had experience

2. **Which strategies does your company employ in planning for requesting the use of the single pathway (or in combination with multiple FRPs within and across countries)? Please write an 'X' in all applicable boxes and specify if 'case-by-case'.**

Strategy specific to each pathway	Requested for all assets	Requested on case-by-case basis	If case-by-case, please specify the selection criteria
FDA Breakthrough Therapy			
FDA Fast Track			
EMA PRIME			
PMDA Sakigake			

Please provide any additional comments below

3. Please complete a SWOT analysis for each FRP below, taking into account the following factors:

- meeting the requirements for each pathway from development through to post-approval
- internal resources and preparations that need to be considered for the FRP
- external interactions with the agency
- impact of FRP on subsequent approval as well as reimbursement

a) FRP: FDA Breakthrough therapy	
Strengths: 1. 2. 3.	Weaknesses: 1. 2. 3.
Opportunities: 1. 2. 3.	Threats: 1. 2. 3.

Please suggest some potential solutions to the threats listed (for FDA BTD):

1.
2.
3.

b) FRP: FDA Fast Track	
Strengths: 1. 2. 3.	Weaknesses: 1. 2. 3.
Opportunities: 1. 2. 3.	Threats: 1. 2. 3.

Please suggest some potential solutions to the threats listed (for FDA Fast Track):

1.
2.
3.

c) FRP: EMA PRIME	
Strengths: 1. 2. 3.	Weaknesses: 1. 2. 3.
Opportunities: 1. 2. 3.	Threats: 1. 2. 3.

Please suggest some potential solutions to the threats listed (for EMA PRIME):

1.
2.
3.

d) FRP: PMDA Sakigake	
Strengths: 1. 2. 3.	Weaknesses: 1. 2. 3.
Opportunities: 1. 2. 3.	Threats: 1. 2. 3.

Please suggest some potential solutions to the threats listed (for PMDA Sakigake):

1.
2.
3.

4. Does the FRP designation impact how the product is perceived by the following stakeholders. Please write an X in the relevant boxes, where '-' = negative impact, '-/+' = mixed impact, '+' = positive impact, '0' = no impact. Please provide any comments to support your responses.

	Stakeholder perception																							
	Your company				Patients				Physicians				Other Regulators				HTA /Payers				Investors			
	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0	-	-/+	+	0
FDA Breakthrough Therapy																								
FDA Fast Track																								
EMA PRIME																								
PMDA Sakigake																								
Comments																								

5. **If you received a regulatory approval with any of the designations, did advertising/promotion reflect any specific aspects of the FRP? Please write an 'X' in all the relevant boxes, as well as any additional comments.**

	Yes	No	Comment
FDA Breakthrough Therapy			
FDA Fast Track			
EMA PRIME			
PMDA Sakigake			

6. **What is your perceived overall return on investment (ROI) for the sponsor for each FRP? Please write down the score for each FRP, where 1= poor, 3= average, 5= excellent. Please feel free to provide any comments to support your responses.**

	ROI score (1= poor, 3= average, 5= excellent)	Comment
FDA Breakthrough Therapy		
FDA Fast Track		
EMA PRIME		
PMDA Sakigake		

SI 2: SWOT analyses

FDA Breakthrough Therapy Designation

Strengths	**Weaknesses**
Intensive FDA guidance on an efficient drug development program, beginning as early as phase 1 Faster development time Expedited timing of agency feedback Focus on products for unmet medical need Assignment of "A-team" talent reviewers Accelerates getting important new therapies to patients Confidentiality is useful and important for intellectual property rights.	Upfront resources required; Project teams need to be ready for the demands of increased agency feedback, interactions, request for information Ability to optimize manufacturing processes in time for marketing application submissions Public perception of lowering the bar for approval Alignment within FDA disciplines is sometimes missing; Varying levels of adoption across review divisions and therapeutic areas Takes away FDA resources from non-BTD drugs for serious and life-threatening chronic diseases that do not meet the unmet medical need requirement Higher bar as compared to Fast Track, as preliminary clinical evidence is required (however, the features for BTD are greater, so greater reward for meeting the higher bar) No similar opportunities in other regions, can cause staggered development, submissions
Opportunities	**Threats**
Increased opportunities for agency interactions and scientific advice; builds relationships Higher likelihood for priority review and/or rolling review; increases probability of approval on first cycle review Flexible and pragmatic approaches encouraged External visibility that product in development may provide substantial improvement over existing therapy Shared learning about other BT applications Greater possibility for informal interactions Should be expanded to other types of products/conditions Provides opportunity for alignment with EMA PRIME	Stretched FDA resources may limit effectiveness of the program; reduces manpower for non-BTD products No incentive for FDA to approve early, only for meeting or exceeding PDUFA review time Level of evidence to support BTD has increased with time (notably in oncology); expectation for strength of data needed is not always clear, and seemingly differs across therapeutic areas Designation can be withdrawn if entire body of data is no longer supportive There is the potential for FDA to withdraw designation based on competitor's product data and FDA's decision to rescind designation may not be transparent to the company with the rescinded designation. Reimbursement barriers for streamlined clinical development program

FDA Fast Track

Strengths	**Weaknesses**
Increased opportunities for scientific interactions with the authority especially with preclinical and when minimal clinical data exist (less clinical data than required for BTD) Focus on unmet need As the requirements for strength of data are not as high, it's clearer when granting of the designation is likely Clinical data are not required to receive the designation Possibility for Rolling Review as resources permit and user fees paid	Benefits of this designation are not fully understood for many in the industry, especially with the other 21st Century Cures initiatives and FDARA performance goals now available. Communication is not at same level as breakthrough; interactions with FDA not often granted despite FT designation No tangible benefit in terms of expediting therapies for patients Takes away FDA resources from non-FT drug Viewed as a "lower priority" than Breakthrough designation and may lead to less agency engagement
Opportunities Increase resourcing to allow reviews to commence on time Designation often receives favourable investor attention Possibility of reducing development time Expand use to other categories of medicines	**Threats** Designation can be rescinded Limited by FDA manpower Designation can be withdrawn if entire body of data is no longer supportive of potential benefit Keeping FTD relevant considering BTD, as when viewed side by side, BTD is seen as having more value than FTD; may have passed its usefulness Not clear what value Fast Track yields on its own for a product given all the other innovative initiatives Public opinion does not understand well and may believe standards are compromised

EMA PRIME Designation

Strengths	**Weaknesses**
Increased opportunities for interactions and advice from the health authority; Multi-stakeholder F2F meetings Holistic vision and helpful recommendations at PRIME kick-off meeting; continuity of advice throughout the process Pilot offers companies a pre-call prior to formal PRIME scheme application Transparency of products accepted into PRIME and overall PRIME metrics Early confirmation of Rapporteur. Enhanced Rapporteur engagement; clarity of who to contact Possibility of early approval vs. standard pathways	The understanding of PRIME and its benefits not so clear as for the FDA breakthrough No clear guidance what does meet the criteria and what not Upfront resources required by sponsor; Resources at EMA seem to be limiting the number of designations approved Small window of opportunity to apply; can only be obtained early in development, which limits its utility in accelerating getting therapies to patients Preparation for PRIME designation takes too long especially when there is a high risk of denial based on other products precedents. Often it is faster to prepare and seek Scientific Advice Late feedback on potential meeting discussion topics at kick-off meeting Limited experience and lower acceptance rate compared to US BTD Not available to large companies early in a product's development Not available for new indications Challenges in coordinating meeting with EMA teams
Opportunities	**Threats**
Open PRIME to all sponsors and for all indications Opportunity to share disease expertise with the Rapporteur and the assessment team which assists in keeping the future assessment focused More opportunities for agency interactions Link to Accelerated assessment Make process more dynamic like the US BTD procedure Seek ways of improving flexibility HTAs involvement at the time of designation to, for instance, cross check the unmet medical need	Inflated expectation of what PRIME can deliver PRIME does not offer much more than normal development pathways for big companies; losing interest; Little perceived advantage compared to normal scientific advice. Limited level of resourcing / acceptance caused EU to be viewed as less supportive of innovation Need for EMA to better gather aggregated data and publicize results on the benefits of PRIME for product development/authorization Sudden changes to development/regulatory strategy if emerging data leads to withdrawal of PRIME designation/support Lack of alignment with US and Japan to support global acceleration; PRIME and BTD not always granted for the same products (global development plan not possible) No mechanism for accelerating additional indications Lack of engagement of many HTA bodies

PMDA Sakigake Route

Strengths	**Weaknesses**
Solid criteria and a well-established scheme Substantive Preapplication review Extended exclusivity period (max. 10yrs) and price premium reimbursement price (10-20% more); Strong positioning in Japan market (first in class in Japan); Extension of re-examination period Faster development and launch; Promoted/ accelerated patient access to innovative products (priority rolling regulatory review within 6 months) increased interactions with the agency with a designated review concierge; Consistent support by PMDA throughout development until approval; Prioritized consultation Open to new indications Reducing submission lag	Resource intensive for the sponsor Competitive designation as a pilot program currently; Sakigake scheme has not been legalized Application/designation timing is not flexible (once a year) Limited acceptance of English documents (i.e., global unified dossier) No discount of filing package – different from conditional approval Limited experience and lower acceptance rate compared to US BTD Difficult to adjust the timing of filing in Japan, in case where it is also designated as PRIME/BT Earlier development required in Japan ahead of the rest of world; Required to be the 1st submission for regulatory approval in the world Challenge to prepare CMC data package; Application delay due to delayed GMP inspection preparation PMDA may not accept many applications due to the limited resources
Opportunities Greater use of the pathway for other types of products Relaxing the requirement for earlier development in Japan ahead of the world	**Threats** Becoming more and more competitive due to increase in submission volume It is not necessarily given the designation even if it satisfies the criteria, due to resource constraints of PMDA reviewers workload If a similar competitor is approved earlier than SAKIGAKE project, the designation is cancelled Submission readiness; Most of dossier needs to be ready at the pre-NDA consultation meeting 4 months prior to the JNDA to complete prioritized review within 6 months. Preparation for commercial manufacturing Concurrent designation of FRP in other regions; May difficult to achieve at least same day filing (1st filing in the world) GMP inspection in parallel to review may be hurdles for manufacturers