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EXPEDITING ACCESS TO NOVEL/MEDICINAL PRODUCTS IN THE UNITED STATES AND EUROPE

A LIVE WEBINAR ON TUESDAY, APRIL 26, 2022

10:00 AM - 11:00 AM EDT (15:00 -16:00 BST)

AGENDA

Understand when and how to apply for the following expedited pathways with FDA and EMA:

- Breakthrough Therapy (BT)
- PRIME (PRIority MEdicines)
- Fast Track (FT); QIDP; RMAT; Priority Review
- Accelerated Assessment(AA), Emergency Use Authorization (EUA), Certification of quality and nonclinical for SME ATMPs
- Accelerated Approval and Conditional Marketing Authorisation (CMA)

Consider real-world examples of increased efficiency with submitting pathways requests

FDA DEFINITION:
SERIOUS CONDITION

". . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self- limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

Source: https://www.fda.gov/media/86377/download

EMA DEFINITION:
SERIOUS CONDITION

"Whereas a life-threatening disease is relatively easy to describe based on figures of mortality and life expectancy, justifying that a disease is seriously debilitating will have to consider morbidity and its consequences on patients' day-to-day functioning. For a disease to be considered seriously debilitating it would need to have a well-established major impact on patients' day-to-day functioning either already early in the course of the disease, or in the later stages. These aspects should be quantified in objective terms, as far as possible. Furthermore, serious debilitation, or fatal outcome should be a prominent feature of the target disease and therapeutic indication, i.e. affect an important portion of the target population."

Source: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-scientific-application-practical-arrangements-necessary-implement-commission-regulation-ec/2006-conditional-marketing-authorisation-medicinal-products-human-use-falling_en.pdf

UNMET MEDICAL NEED CRITERIA

WHERE THERE IS **NO AVAILABLE THERAPY**

EMA defines as

"*there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected*"

WHERE THERE IS AVAILABLE THERAPY BUT THE INVESTIGATIONAL AGENT:

- Lessens serious outcome of the condition that is not seen with or is better than available therapy
- Can be used effectively with other critical agents that cannot be combined with available therapy
- Provides efficacy comparable to available therapy while avoiding serious toxicity that occurs with available therapy, (2) avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious condition, or (3) reducing the potential for harmful drug interactions
- Demonstrates a documented benefit that is expected to lead to an improvement in serious outcomes

ONLY AVAILABLE THERAPY HAS ACCELERATED APPROVAL

For FDA only

- Only available therapy was approved under the Accelerated Approval program based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not yet been verified

BREAKTHROUGH THERAPY (BT) DESIGNATION

Timing & Process

- Can be submitted with IND, but need for clinical evidence precludes this in most cases
- Ideally submitted prior to pivotal study
- FDA response in 60 days

Qualifying Criteria

- Serious condition
- Preliminary clinical evidence that the drug may demonstrate **substantial improvement** on a clinically significant endpoint(s) over available therapies

Benefits

- Intensive guidance on efficient drug development
- Initial Comprehensive Multidisciplinary BT meeting
- Organizational commitment
- Possibility for Expedited Review of BTD Marketing Applications (Action planned at least one month prior to PDUFA goal date)
- Rolling review

BT DESIGNATION ISN'T ALWAYS GRANTED

BT Designation Application Success Rates

FY 2013 - First Full Program Year)	
Granted:	31 (33.7%)
Denied:	52 (56.5%)
Withdrawn:	9 (9.8%)

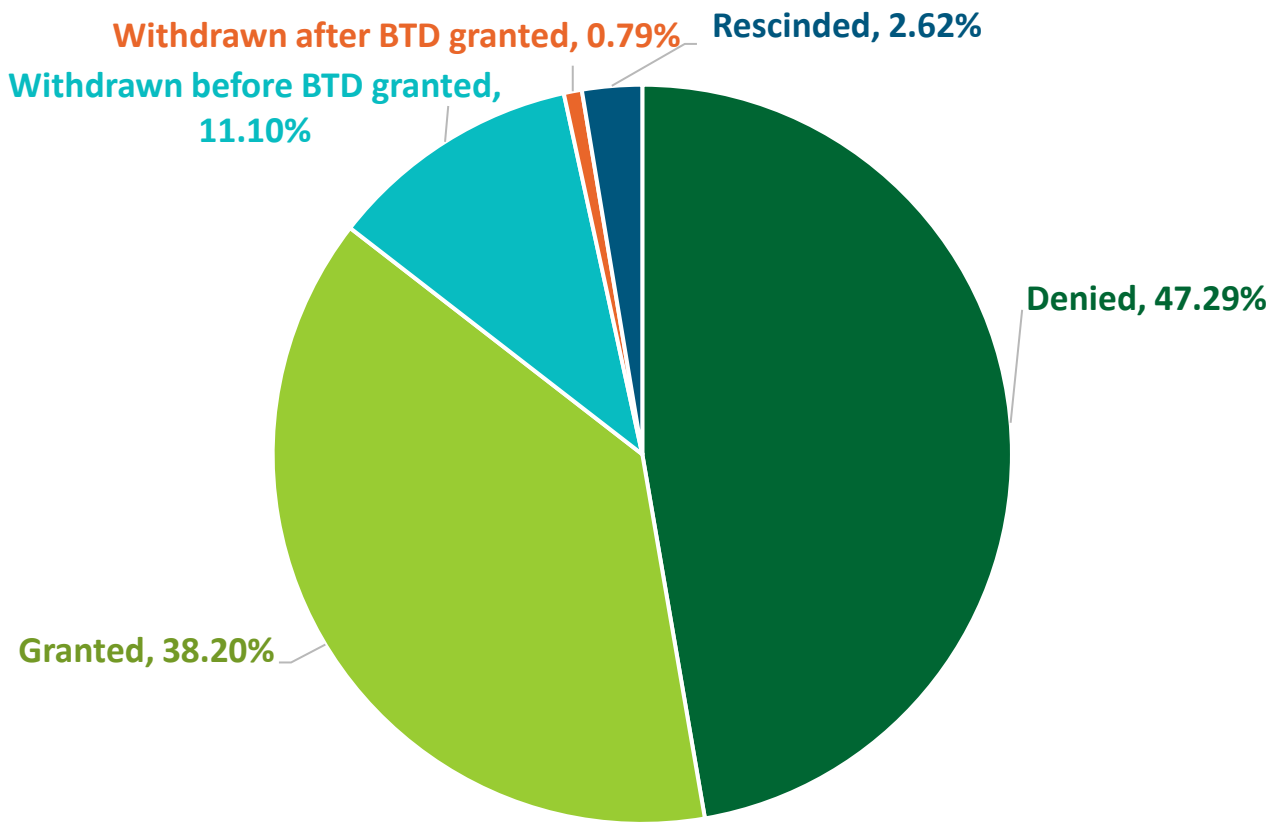
FY 2021	
Granted:	4 (44.4%)
Denied:	5 (55.6%)
Withdrawn:	0 (0%)

Source: https://www.brookings.edu/events/breakthrough-therapy-designation-exploring-the-qualifying-criteria/; https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cber&id=CBER-All-Number-of-Breakthrough-Therapy-Requests-Received-and-Approvals

BT DESIGNATION APPLICATION SUCCESS RATES

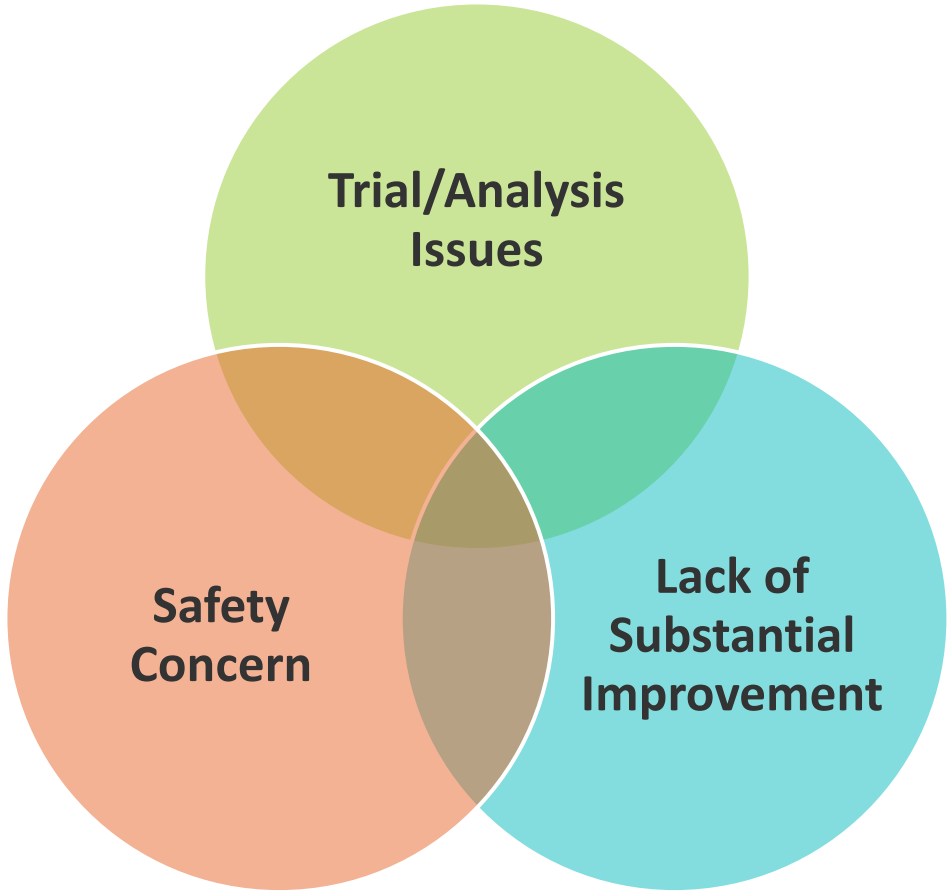
Cumulative from FY 2013 – FY 2020

The FDA has received **1,138** requests for breakthrough therapy designation as of 31 March 2021



Source: https://pink.pharmaintelligence.informa.com/PS144170/Half-Of-US-FDAs-Breakthrough-Therapy-Designations-Have-Resulted-In-Approval

REASONS FOR DENIAL OF BT DESIGNATION



Denials N=109
Reasons for Denial*

Trial/Analysis Issues	**78 (72%)**
Trial Design Issues	45 (41%)
Sample Issues	39 (36%)
Endpoint Issues	29 (27%)
Results too preliminary	19 (17%)
Flawed post-hoc analysis	17 (16%)
Lack of Substantial Improvement	**58 (53%)**
Lack of Data	18 (17%)
No clinical data	4 (4%)
Incomplete data	14 (13%)
Safety Concerns	**12 (11%)**
Miscellaneous	14 (13%)
Not serious condition	2 (2%)
Other	12 (11%)

* Totals exceed 100% as many denials cited multiple reasons for denials.

Source: https://www.brookings.edu/events/breakthrough-therapy-designation-exploring-the-qualifying-criteria/

BREAKTHROUGH THERAPY EXAMPLES

PRIORITY **ME**DICINES (PRIME)

Timing & Process

- PRIME eligibility should be granted as early as possible, with preliminary clinical evidence (phase 2 studies) demonstrating the promising activity of the medicinal product and its potential to address to a significant extent an unmet medical need (Proof of concept).

Qualifying Criteria

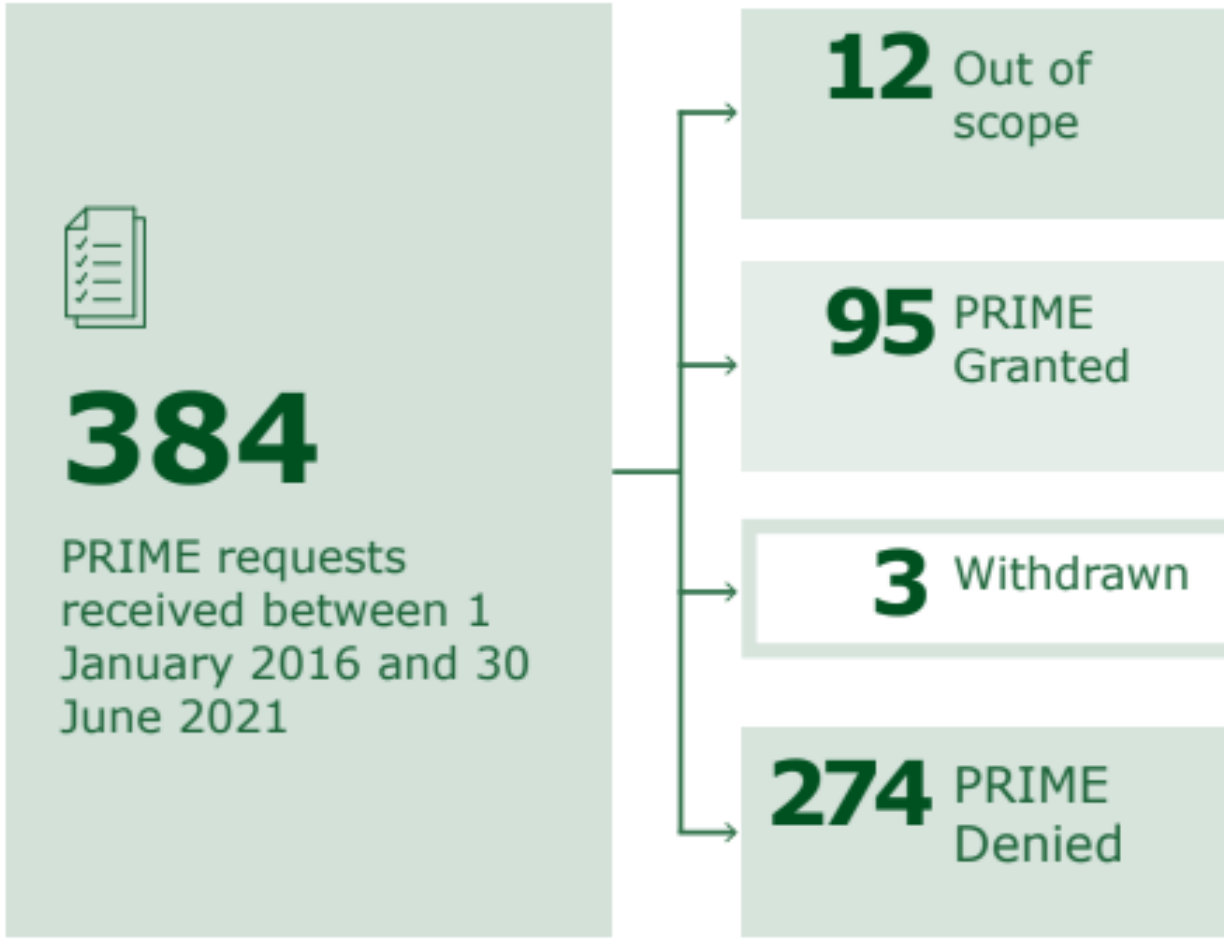
- Medicinal product is of major public health interest and a therapeutic innovation.
- Should target conditions where there is an unmet medical need or, the candidate will have a major therapeutic advantage.
- Data available to support a request for eligibility should support the claim that the product has the potential to bring a major therapeutic advantage to patients, through a clinically meaningful improvement of efficacy.

Benefits

- Appoint a rapporteur from the (CHMP) or from the (CAT) to provide continuous support and a dedicated contact point.
- Organize a KOM with the rapporteur and a multidisciplinary group of experts.
- Guidance on the overall development plan and regulatory strategy
- Provide scientific advice
- Potential for Accelerated Assessment at the time of an MAA.

OVERALL PRIME ACCEPTANCE IS LOW | #GRANTED VS. DENIED

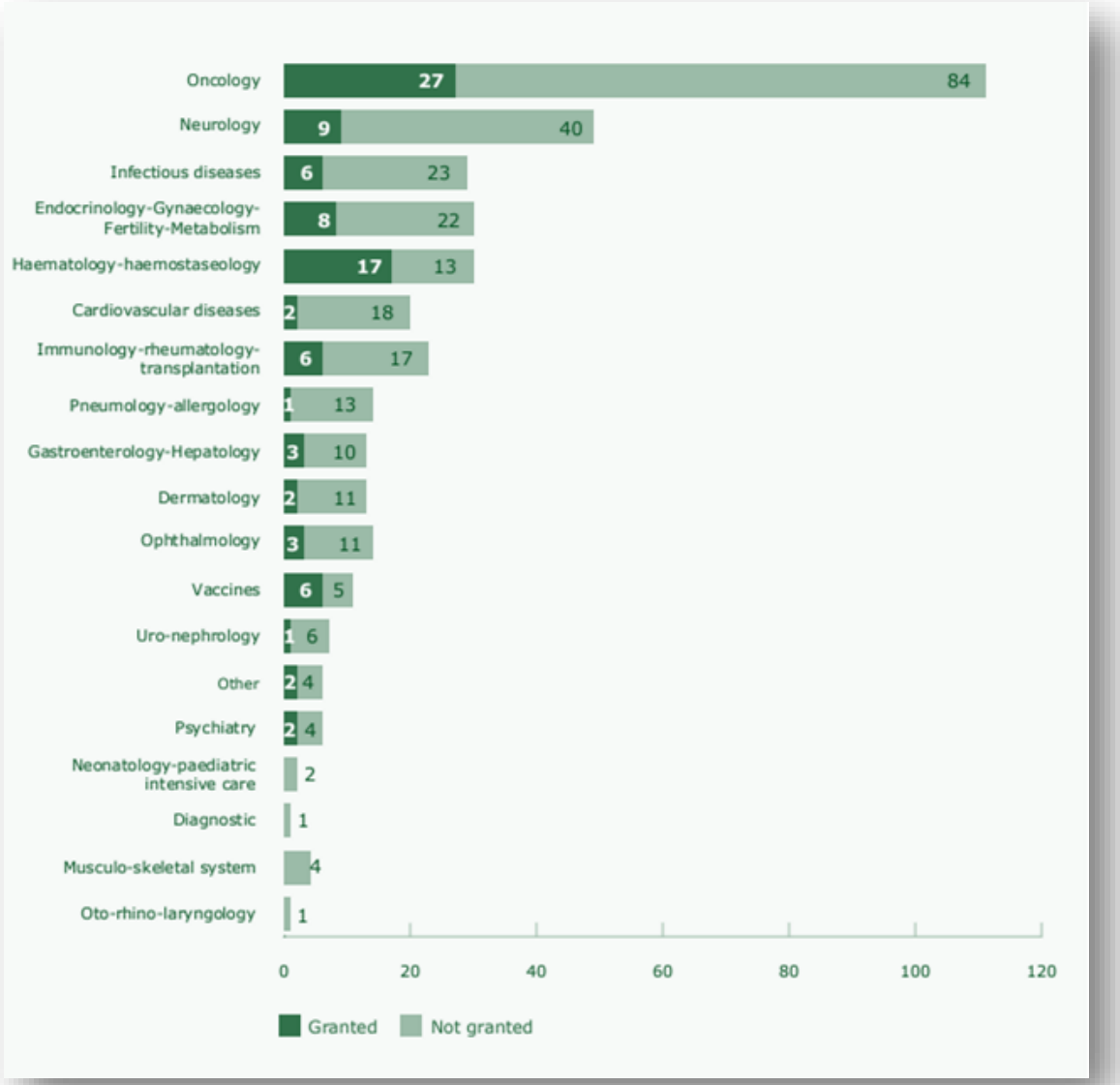
In the period 7 March 2016 to 30 June 2021, a total of 384 requests for PRIME eligibility were received, 372 were validated and 95 granted, corresponding to an **overall acceptance rate of 25%.**



Source: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

PRIME # OF GRANTED VS. DENIED BY THERAEPUTIC AREAS

Across therapeutic areas, the **success rate ranges between 20-30%.**



Source: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

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PRIME EXAMPLES

OTHER FDA EXPEDITED PROGRAMS & THEIR BENEFITS

Fast Track

- Actions to expedite development and review (opportunities for frequent interactions with the review team for a Fast Track product)
- Rolling review (submit documents for application in a rolling fashion)

Qualified Infectious Disease Program

- 5-year exclusivity extension
- Priority review (first application)
- Fast Track designation (must be specifically requested)

Regenerative Medicine Advanced Therapy

- All breakthrough therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints
- Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements

Priority Review

- Shorter clock for review of marketing application
  - (6 months compared with the 10-month standard review)
- Nonclinical or clinical data to demonstrate the potential to address unmet medical need

COMPARISON AND BENEFITS OF EUA, AA AND SME ATMPS

Emergency Use Authorization

- FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases
- Must be chemical, biological, radiological and nuclear (CBRN) threats
- When “emergency status” ends, so does EUA and must proceed with full approval

Accelerated Assessment

- Request to EMA 2-3 months prior to submitting MAA
- Reduces timeframe of CHMP review of the MAA, specifically from 210 to 150 days
- A pre-submission meeting is advised 6-7 months prior to MAA

Certification of quality and nonclinical for SME ATMPs

- Giving the SMEs an incentive to develop ATMPs
- Stand-alone evaluation procedure, which is independent from a future MAA
- Could facilitate the evaluation of any future application for CTA or a MAA

COMPARISON AND BENEFITS OF ACCELERATED APPROVAL AND CMA

Accelerated Approval

- FDA may grant AA, but not a formal request
- Confirmatory trial needed
- Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit

Conditional Marketing Authorisation (CMA)

- EMA is notified about intention to request a CMA as part of the "letter of intent" sent in advance of the submission of the application for marketing authorisation
- Best practice to run a confirmatory trial, and must get annual renewal
- Must fully demonstrate positive benefit-risk

AA AND CMA EXAMPLES

WHY CONSIDER EXPEDITED PATHWAYS/DESIGNATIONS?

The potential to shorten the clinical development and/or regulatory approval time

Name	Agency	Benefit
Breakthrough Therapy (BT)	FDA	Shortened clinical development time
PRIME (PRIority MEdicines):	EMA	Shortened clinical development time
Fast Track (FT)	FDA	Both timelines possibly shortened- clinical development and review
Qualified Infectious Disease Product Designation (QIDP)	FDA	Get Fast Track designation and 5-year exclusivity extension
Regenerative Medicine Advanced Therapy Designation (RMAT)	FDA	Shorten development and review timelines
Priority Review (PR)	FDA	Shorter review timeline
Accelerated Approval (AA)	FDA	Shortened development and approval time
Emergency Use Authorization (EUA)	FDA	Quick approval during "emergency" until full approval
Accelerated Assessment	EMA	Assigned Rapporteur and shorter review cycle
Conditional Marketing Authorization (CMA)	EMA	Earlier approval using less data – can shorten development and approval time


QUESTIONS???

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BACKGROUND/REFERENCES

REFERENCE LINKS

DESIGNATION NAME	LINK
Breakthrough Therapy (BT) |	https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy
PRIME (PRIority MEdicines)	https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
Fast Track (FT)	https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track
Qualified Infectious Disease Product Designation (QIDP)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualified-infectious-disease-product-designation-questions-and-answers
Regenerative Medicine Advanced Therapy Designation (RMAT)	https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation
Priority Review	https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review
Accelerated Approval	https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval
Emergency Use Authorization	https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
Accelerated Assessment	https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment
Conditional Marketing Authorisation (CMA)	https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation