Regulatory Incentives for Innovation: The FDA's Breakthrough Therapy Designation[1]

Amitabh Chandra[*,†], Jennifer Kao[§], Kathleen Miller[‡] & Ariel Dora Stern[†]

[*]Harvard Kennedy School
[†]Harvard Business School
[§]UCLA Anderson
[‡]US Food and Drug Administration

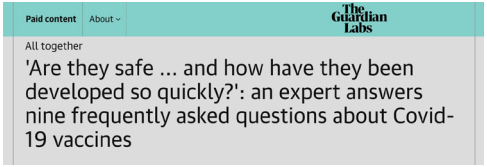
June, 2022

[1]Acknowledgements: this project is supported by the Harvard Business School Division of Research and Faculty Development (to Chandra and Stern), the Kauffman Foundation (Stern), and NIA grant numbers T32-AG000186 and R24AG048059 to the National Bureau of Economic Research (Kao)

Motivation

- New product development: by nature risky, costly endeavor
- Manufacturers must strike a balance between **pushing a new product to market** and **gathering information about quality**
- Why does this sound familiar?

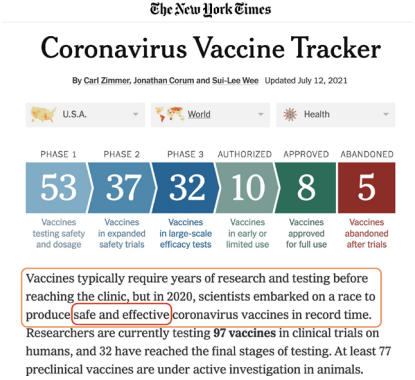
Motivation


Paid content About

The Guardian Labs

All together

'Are they safe ... and how have they been developed so quickly?': an expert answers nine frequently asked questions about Covid-19 vaccines


The New York Times

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated July 12, 2021

U.S.A. World Health

PHASE 1	PHASE 2	PHASE 3	AUTHORIZED	APPROVED	ABANDONED
53	37	32	10	8	5
Vaccines testing safety and dosage	Vaccines in expanded safety trials	Vaccines in large-scale efficacy tests	Vaccines in early or limited use	Vaccines approved for full use	Vaccines abandoned after trials

Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **97 vaccines** in clinical trials on humans, and 32 have reached the final stages of testing. At least 77 preclinical vaccines are under active investigation in animals.

Motivation

- In a 2020 *Nature* article, Dan Barouch, director of the Center for Virology and Vaccine Research at Harvard Medical School: **with sufficient resources, "the development process can be accelerated substantially without compromising on safety."**
- However, the recent phenomenon of swift, high-quality Covid-19 vaccine development is not unique
- **This paper:** We examine the impact of a nearly 10-year old regulatory incentive program on time-to-market and product quality

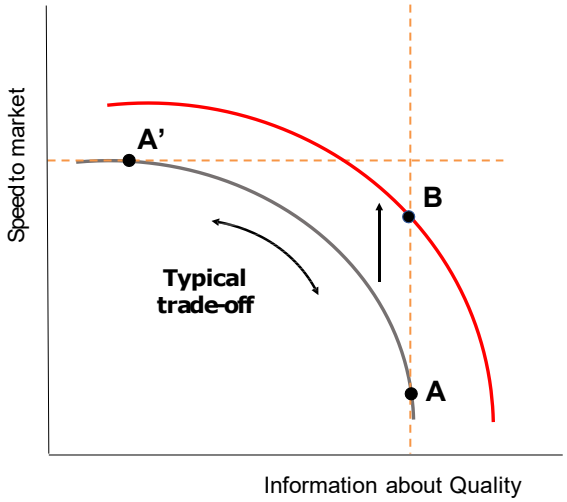
Shifting the Trade-off Curve

- Health care regulators: provide economic incentives; speed of access vs. information about new therapies
- Programs targeting review processes decrease time to market, but may be associated with more adverse events [e.g., Olson, 2008; Philipson et al., 2008; Stern et al., 2017]
- Is it possible to shift out the "speed-information trade-off curve"?
- **Breakthrough Therapy Designation, "BTD"**
  - Growing use since launch in 2012; Expanding to devices; EMA's

  (related) "PRIME" program launched in the interim ▸ Details

Conceptual Framework

Can We Do Better?



Research Question

Can the Speed-Information Trade-off Curve Be Shifted Out?

BTD program: pathway to make new drug commercialization process faster and more transparent for innovator firms

Consider the impact of BTD program on:

1. Time to market
   - Length of regulatory approval
   - Length of clinical development period (multiple measures)
2. Product safety
   - Drug adverse event rates (more informative than levels!)

Preview of Results

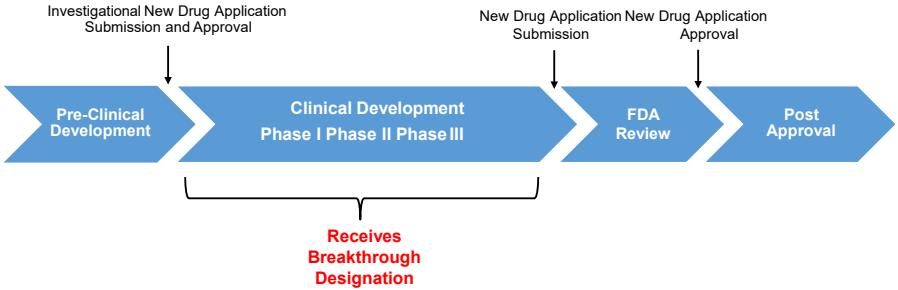
- Statistical selection = big, obvious problem.
  - Solution: **Construct control group** of historical "breakthrough" drugs
- BTD drugs experience **shorter regulatory approval** periods
  - However, results **driven by participation in other accelerated FDA programs** →BTD itself does not decrease regulatory approval time
- BTD **shortens clinical development times** *prior* to regulatory submission; in particular, large decreases in length of late-stage trials
- **Little evidence that BTD drugs are less safe**

Breakthrough Therapy Designation

- Established under Food and Drug Administration Safety and Innovation Act of 2012
- **Criteria**: Preliminary clinical evidence of substantial improvement over available therapies.
- **Unique features***
  - Intensive guidance on efficient drug development
    - *"Intensive Guidance....Beginning... Early"; "taking steps to ensure that the design of clinical trials is...efficient."*
    - *"the Secretary shall...expedite the development and review"*
  - Organizational commitment
    - *"involving senior managers and experienced review staff...in a collaborative, cross-disciplinary review"*

*See Darrow, et al. (2018) andFDA (www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy)

Typical Timeline of Drug Development, FDA Programs

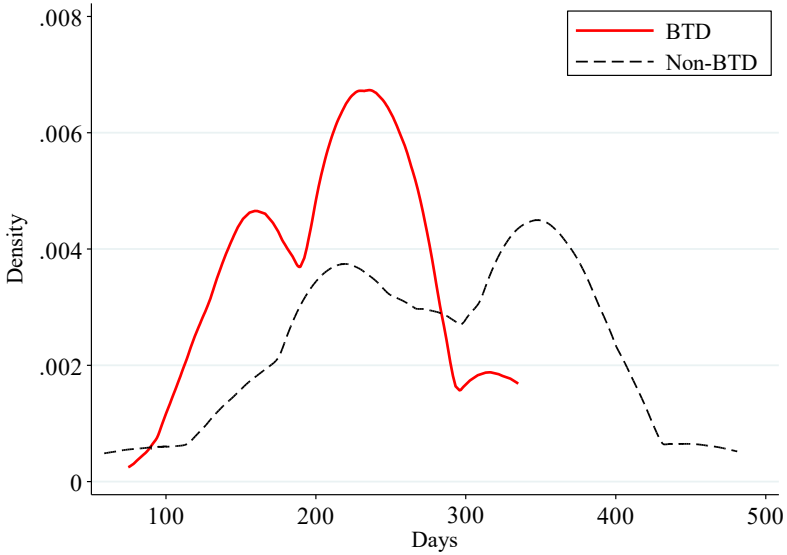


▸ Summary of FDA programs

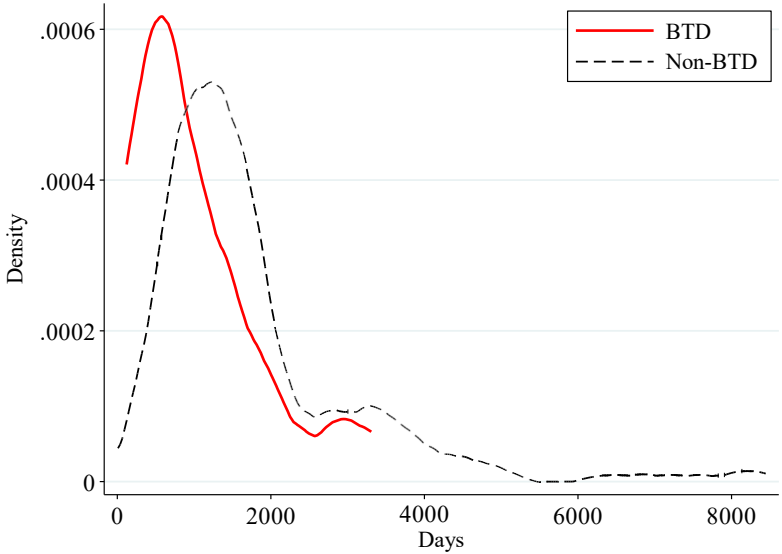
Data

- All drugs first approved by FDA from 2006-2018
  - Focus on New Molecular Entities
  - FDA expedited programs – e.g., Breakthrough designations 2012-2018
  - Commercializing firm and drug characteristics – e.g., firm public/private status, indication (ATC)
- Outcomes - 4 key datasets:
  1. Drug approval times (Drugs@FDA)
  2. Clinical development times (Drugs@FDA, ClinicalTrials.Gov)
  3. Adverse events data (FDA Adverse Event Reporting System)
     - E.g., death, hospitalizations, pain
  4. Prescription counts: used as a "denominator" for adverse event frequencies (Optum Claims)

Motivating Facts: Time in Regulatory Review



Motivating Facts: Time in Clinical Development



Summary Statistics

	BTD N = 60		Non-BTD N = 336		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Priority Review (0/1)	0.98	0.13	0.45	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.27	0.45	0.00**
Accelerated Approval (0/1)	0.35	0.48	0.09	0.28	0.00***
Boxed Warning (0/1)	0.23	0.43	0.38	0.49	0.03**
ATC: Cancer (0/1)	0.57	0.50	0.29	0.45	0.00***
Private Firm (0/1)	0.23	0.43	0.29	0.45	0.41
Panel B. Time-to-Market (Months)					
Regulatory Review	7.13	1.97	8.66	3.35	0.00***
Phase 2 to Regulatory Review	58.48	33.34	74.87	38.36	0.00**
Phase 3 to Regulatory Review	32.51	26.57	49.71	36.07	0.00***
Panel C. Adverse Event Rates					
Within 3 Months	4.43	5.87	1.79	3.75	0.00**
Within 5 Months	7.39	10.42	2.16	6.02	0.00***

Summary Statistics

	BTD N = 60		Non-BTD N = 336		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Priority Review (0/1)	0.98	0.13	0.45	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.27	0.45	0.00**
Accelerated Approval (0/1)	0.35	0.48	0.09	0.28	0.00***
Boxed Warning (0/1)	0.23	0.43	0.38	0.49	0.03**
ATC: Cancer (0/1)	0.57	0.50	0.29	0.45	0.00***
Private Firm (0/1)	0.23	0.43	0.29	0.45	0.41
Panel B. Time-to-Market (Months)					
Regulatory Review	7.13	1.97	8.66	3.35	0.00***
Phase 2 to Regulatory Review	58.48	33.34	74.87	38.36	0.00**
Phase 3 to Regulatory Review	32.51	26.57	49.71	36.07	0.00***
Panel C. Adverse Event Rates					
Within 3 Months	4.43	5.87	1.79	3.75	0.00**
Within 5 Months	7.39	10.42	2.16	6.02	0.00***

Summary Statistics

	BTD N = 60		Non-BTD N = 336		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Priority Review (0/1)	0.98	0.13	0.45	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.27	0.45	0.00**
Accelerated Approval (0/1)	0.35	0.48	0.09	0.28	0.00***
Boxed Warning (0/1)	0.23	0.43	0.38	0.49	0.03**
ATC: Cancer (0/1)	0.57	0.50	0.29	0.45	0.00***
Private Firm (0/1)	0.23	0.43	0.29	0.45	0.41
Panel B. Time-to-Market (Months)					
Regulatory Review	7.13	1.97	8.66	3.35	0.00***
Phase 2 to Regulatory Review	58.48	33.34	74.87	38.36	0.00**
Phase 3 to Regulatory Review	32.51	26.57	49.71	36.07	0.00***
Panel C. Adverse Event Rates					
Within 3 Months	4.43	5.87	1.79	3.75	0.00**
Within 5 Months	7.39	10.42	2.16	6.02	0.00***

Summary Statistics

	BTD N = 60		Non-BTD N = 336		
	Mean (1)	SD (2)	Mean (3)	SD (4)	P-Value (5)
Panel A. Drug Characteristics					
Priority Review (0/1)	0.98	0.13	0.45	0.50	0.00***
Fast Track (0/1)	0.50	0.50	0.27	0.45	0.00**
Accelerated Approval (0/1)	0.35	0.48	0.09	0.28	0.00***
Boxed Warning (0/1)	0.23	0.43	0.38	0.49	0.03**
ATC: Cancer (0/1)	0.57	0.50	0.29	0.45	0.00***
Private Firm (0/1)	0.23	0.43	0.29	0.45	0.41
Panel B. Time-to-Market (Months)					
Regulatory Review	7.13	1.97	8.66	3.35	0.00***
Phase 2 to Regulatory Review	58.48	33.34	74.87	38.36	0.00**
Phase 3 to Regulatory Review	32.51	26.57	49.71	36.07	0.00***
Panel C. Adverse Event Rates					
Within 3 Months	4.43	5.87	1.79	3.75	0.00**
Within 5 Months	7.39	10.42	2.16	6.02	0.00***

Matching, Part 1

- Start with post-2012 designated (true) BTDs & non-BTDs
- Implement historical algorithmic matching to pre-2012 drugs
- Match with replacement on drug and firm characteristics–e.g., disease, sponsor public/private status
- Goal: Identify historical “treatment” (imputed BTD) and “control” (imputed non-BTD) groups for diff-in-diff

Matching, Part 2

Matching designated non-BTDs and BTDs to pre-2012 drugs:

	Total	Non-BTD	BTD	Other
Pre-2012	169			
Post-2012	227	167 (True Non-BTD)	60 (True BTD)	
Total	396			

Matching, Part 2

Matching designated non-BTDs and BTDs to pre-2012 drugs:

	Total	Non-BTD	BTD	Other*
Pre-2012	169	95 (Imputed Non-BTD)	29 (Imputed BTD)	45 (Other)
Post-2012	227	167 (True Non-BTD)	60 (True BTD)	
Total	396	262	89	45

*"Other" includes pre-2012 drugs with no matches.

Difference-in-Differences

For drug *d*:

$$Outcome_d = \alpha + \beta BTD_d + \lambda BTD_d \times Post2012_d + Controls_d + \epsilon_d$$

- BTD_d = Indicator for BTD (true or imputed)
- $Post2012_d$ = Indicator for whether drug approval year $>$ 2012
- $Controls_d$ = Drug-specific controls (e.g., small molecule/biologic, ATC, regulatory programs, etc.)

Impact on Time-to-Market

	Reg Review		Phase III to Reg Review		Phase II to Reg Review	
	(1)	(2)	(3)	(4)	(5)	(6)
BTD	-0.276***	-0.065	-0.304**	-0.116	-0.142	-0.117
	(0.071)	(0.083)	(0.123)	(0.133)	(0.103)	(0.113)
BTD x Post-2012	0.012	-0.059	-0.292*	-0.275*	-0.256*	-0.194
	(0.084)	(0.084)	(0.176)	(0.155)	(0.131)	(0.122)
NDA		-0.112**		0.019		-0.004
		(0.039)		(0.089)		(0.075)
Priority Review		-0.234***		0.020		0.079
		(0.045)		(0.100)		(0.080)
Private Firm		0.033		0.155*		0.126*
		(0.047)		(0.090)		(0.066)
Mean	258.32	258.32	1472.70	1472.70	2237.01	2237.01
Controls: DrugCharacteristics	N	Y	N	Y	N	Y
Controls: Disease	N	Y	N	Y	N	Y
Observations	351	351	331	331	302	302
log likelihood	-2098	-2071	-2676	-2640	-2501	-2478

- BTD leads to a 24% decline in time spent in Phase III Trials

Impact on Safety

	3 Months AE Rates		5 Months AE Rates	
	(1)	(2)	(3)	(4)
BTD	0.178	-0.419	0.780*	0.156
	(0.529)	(0.485)	(0.426)	(0.415)
BTD x Post-2012	0.527	0.899*	0.054	0.678
	(0.606)	(0.541)	(0.515)	(0.476)
NDA		0.479**		0.761**
		(0.232)		(0.240)
Priority Review		0.195		0.314
		(0.257)		(0.246)
Private Firm		-0.799***		-0.766**
		(0.242)		(0.234)
Mean	2.43	2.43	3.31	3.31
Controls: DrugCharacteristics	N	Y	N	Y
Controls: Disease	N	Y	N	Y
Observations	195	195	258	258
log likelihood	-356	-328	-520	-492

Impact on Safety

	3 Months AE Rates		5 Months AE Rates	
	(1)	(2)	(3)	(4)
BTD	0.178	-0.419	0.780*	0.156
	(0.529)	(0.485)	(0.426)	(0.415)
BTD x Post-2012	0.527	0.899*	0.054	0.678
	(0.606)	(0.541)	(0.515)	(0.476)
NDA		0.479**		0.761**
		(0.232)		(0.240)
Priority Review		0.195		0.314
		(0.257)		(0.246)
Private Firm		-0.799***		-0.766**
		(0.242)		(0.234)
Mean	2.43	2.43	3.31	3.31
Controls: DrugCharacteristics	N	Y	N	Y
Controls: Disease	N	Y	N	Y
Observations	195	195	258	258
log likelihood	-356	-328	-520	-492

- Impact of BTD on AE rates do not persist 5 months after approval

Mechanisms: Trial Characteristics

	Phase III Trial Size			Phase III Trial Design Complexity	
	Number of Patients (1)	Number of Facilities (2)	Number of Arms (3)	Randomized (0/1) (4)	Double Blinded Masking (0/1) (5)
BTD	-46.689	-8.732	-0.246	0.145**	0.302**
	(470.354)	(29.122)	(0.249)	(0.073)	(0.101)
BTD x Post-2012	-277.987	-12.681	0.292	-0.208**	-0.559***
	(455.462)	(31.891)	(0.457)	(0.081)	(0.114)
NDA	331.924	5.060	-0.050	0.138**	0.130*
	(276.397)	(18.885)	(0.228)	(0.047)	(0.067)
Priority Review	-603.846	3.873	-0.167	-0.003	0.005
	(524.952)	(22.534)	(0.208)	(0.047)	(0.074)
Private Firm	518.141	16.025	-0.173	-0.095*	-0.081
	(400.226)	(23.886)	(0.170)	(0.052)	(0.059)
Mean	982.56	108.65	2.46	0.88	0.70
Observations	323	277	298	331	322

Mechanisms: Trial Characteristics

	Phase III Trial Size			Phase III Trial Design Complexity	
	Number of Patients (1)	Number of Facilities (2)	Number of Arms (3)	Randomized (0/1) (4)	Double Blinded Masking (0/1) (5)
BTD	-46.689	-8.732	-0.246	0.145**	0.302**
	(470.354)	(29.122)	(0.249)	(0.073)	(0.101)
BTD x Post-2012	-277.987	-12.681	0.292	-0.208**	-0.559***
	(455.462)	(31.891)	(0.457)	(0.081)	(0.114)
NDA	331.924	5.060	-0.050	0.138**	0.130*
	(276.397)	(18.885)	(0.228)	(0.047)	(0.067)
Priority Review	-603.846	3.873	-0.167	-0.003	0.005
	(524.952)	(22.534)	(0.208)	(0.047)	(0.074)
Private Firm	518.141	16.025	-0.173	-0.095*	-0.081
	(400.226)	(23.886)	(0.170)	(0.052)	(0.059)
Mean	982.56	108.65	2.46	0.88	0.70
Observations	323	277	298	331	322

- BTD products tested in Phase III trials that were less complex in design relative to trials of comparable drugs before the BTD was created

Robustness Tests

Some robustness and other tests:

- Comparing true vs. imputed samples →among true vs. imputed BTDs, only one statistically significant difference
- Can assign all double-matched drugs either randomly or only to imputed BTD sample →similar results
- OLS specification →similar results
- Restrict years (e.g., to 2010 and later) →similar results
- Fast Track as a placebo test →no significant results

Summary and Policy Implications

- Breakthrough program decreased clinical development times
  - Phase 3 to submission times decrease by 24% ($5 million/product)
  - Mechanisms: reduced trial design complexity
  - TBD: longer-term implications of these design choices
- Breakthrough drugs do not experience more adverse events (rates) in their first 5 months once selection is accounted for
- However clinical trials look different; may pose challenges for inference and/or comparing products going forward
- Results suggest that targeted policy tools can shorten R&D periods without compromising the quality of new products, implications for clinical practice and reimbursement decisions TBD

Questions & comments welcome!

achandra@hbs.edu
astern@hbs.edu
jennifer.kao@anderson.ucla.edu
kathleen.miller@fda.hhs.gov

Policy Relevance: Growing Use

Back

CDER Breakthrough Therapy Designation Requests Received by Fiscal Year

Cohort: July 9, 2012* - September 30, 2020

Data as of December 31, 2020

Fiscal Year	Total Requests Received	Granted	Denied	Withdrawn
2020	125	58	53	14
2019	156	67	68	21
2018	136	59	60	17
2017	111	50	49	12
2016	106	46	48	12
2015	93	32	43	18
2014	96	31	51	14
2013	92	31	52	9
2012	2	1	1	0

* Breakthrough therapy designation was enacted in the Food and Drug Administration Safety and Innovation Act on July 9, 2012.

Policy Relevance: Expanding to Devices

Back

SEARCH

MedCityNews

Fitbit and NIH boost precision medicine research partnership

Silicon Valley edtech Coursera is trying to change healthcare education

Celgene, following BMS buyout, forms two immuno-oncology partnerships

MEDICAL DEVICES

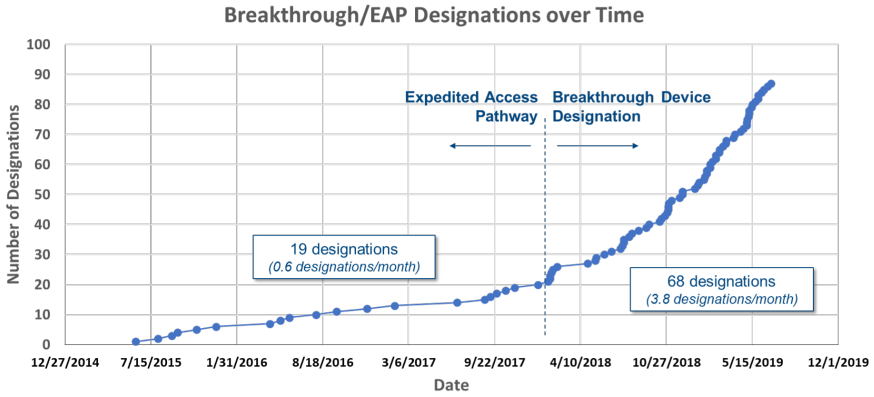
FDA finalizes new breakthrough device designation rule

The larger regulatory modernization efforts, which include updates to the 510(k) regulatory approval pathway and the DeNovo Clearance review process are part of the FDA's Medical Device Safety Action Plan.

By KEVIN TRUONG

Policy Relevance: Devices

Back



Based on publicly available disclosures as of 7/23/19.

Policy Relevance: Both Sides of the Atlantic

Back

Regulatory Focus™

Regulatory Focus™ > News Articles > 7 > FDA and EMA to Hold Workshop on Breakthrough and PRIME Designations

FDA and EMA to Hold Workshop on Breakthrough and PRIME Designations

Posted 31 July 2018 | By Zachary Brennan

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) will hold a workshop on early access approaches, including PRIME and breakthrough designations, on 26 November at the EMA headquarters in London.

EMA said the aim of the workshop is for regulators and industry to discuss "technical quality challenges and scientific and regulatory approaches that could be used to facilitate development and preparation of robust CMC [chemistry, manufacturing and control] data packages," as part of these expedited programs.

Since the PRIME designation launched in March 2016, EMA says it has granted eligibility to 36 programs, 30 of which are for rare diseases and 19 of which are in oncology or hematology. Meanwhile, a review of all therapeutics receiving a breakthrough designation in the US and approved from 2012 to 2017 found a lack of randomization, double-blinding and control groups in pivotal trials supporting approval, a research letter published earlier this month in JAMA found.

Summary of FDA programs*

Back to timeline

Table. Characteristics of the FDA's Expedited Programs for Drugs Treating Serious Diseases[a]

Characteristics	Accelerated Approval Program	Priority Review Program[b]	Fast-Track Program	Breakthrough Therapy Program
Year issued or enacted	1992[c]	1992[d]	1997[e]	2012
Approval based on effect on a surrogate measure or intermediate end point reasonably likely to predict clinical benefit	✓			
Shorter FDA review time		✓		
Rolling review of application			✓	✓
Actions to expedite development process			✓	✓
Organizational commitment and intensive guidance on efficient drug development[f]				✓

*From Hwang, et al. (JAMA, 2017)