RESEARCH LETTER

HEALTH CARE POLICY AND LAW

Fulfillment of Postmarket Commitments and Requirements for New Drugs Approved by the FDA, 2013-2016

Preapproval trials of investigational drugs have limited duration and size and often exclude certain populations. Furthermore, the US Food and Drug Administration (FDA) has recently approved drugs based on fewer clinical trials or less rigorous study designs than in previous years through increased use of expedited pathways[1] and often instructs manufacturers to conduct postapproval studies,[2] which may be delayed or incomplete.[3-5] Because data are lacking about the timeliness of postapproval studies for new drugs approved after 2012, we studied 2013-2016 approvals with follow-up through the end of 2020.

Supplemental content

Methods | This cohort study used Drugs@FDA to identify FDA-approved novel drugs between 2013 and 2016 and all reportable postmarket commitments (PMCs) and postmarket requirements (PMRs) issued at approval. Postmarket requirements are studies required for a drug's approval by 1 of 4 statutes, and PMCs are studies agreed to by the manufacturer as a condition of approval (**Table 1**). We recorded study descriptions and target submission dates and categorized studies in terms of 1 design category (eg, clinical vs observational), 1 temporality category (eg, new vs continuation of existing trial), and up to 3 purpose categories (eg, efficacy, safety).

From archived FDA PMR and PMC databases obtained through the Freedom of Information Act, we collected quarterly FDA-assigned statuses for each PMR and PMC from issuance until fulfillment, release, or the fourth quarter of 2020 (Q4-2020). For studies expected to be submitted or fulfilled by Q4-2020, we determined whether they were early, timely, or late. For studies that were actually submitted or fulfilled by Q4-2020, we calculated projected time to completion, actual time to completion, and lateness. Details are given in the eMethods in the Supplement. Analyses were conducted between June 2021 and July 2022, using Excel, version 2110 (Microsoft Corporation). This study followed the STROBE reporting guidelines. Because no patient information was used, institutional review board approval was not sought.

Results | For all 135 new FDA-approved drugs between 2013 and 2016, we identified 387 PMRs and 87 reportable PMCs (26.5% of 328 total PMCs). Of these 474 PMRs and reportable PMCs, 330 (69.6%) were expected to be completed by Q4-2020, including 282 submitted or fulfilled and 48 due but not completed. Of the 330 to be completed by Q4-2020, 238 (72.1%) were late, including 190 that were completed by Q4-2020.

For 181 requirements under the FDA Amendments Act, 129 (71.3%) were late, as were 44 of 53 (83.0%) Pediatric Research Equity Act (PREA) studies and 9 of 20 (45.0%) accelerated approval confirmatory trials (Table 1). Of 240 studies investigating safety, 173 (72.1%) were late, as were 128 of 183 (69.9%) investigating efficacy, including 85 of 115 (73.9%) and 76 of 103 (73.8%), respectively, investigating safety and efficacy in new subpopulations.

Among 282 studies completed by Q4-2020, median projected time to completion was 8.00 (IQR, 3.00-12.00) quarters, whereas actual time to completion was 10.00 (IQR, 6.00-14.00) quarters (**Table 2**). Median lateness for 190 studies

Table 1. Timeliness of Completion of Postmarket Requirements (PMRs) and Reportable Postmarket Commitments (PMCs) Instituted for New Drugs Approved by the US Food and Drug Administration (FDA), 2013-2016[a,b]

		No. (%)		
	Total No.	Early	On time	Late
Total	330	50 (15.2)	42 (12.7)	238 (72.1)
Reporting authority				
PREA	53	6 (11.3)	3 (5.7)	44 (83.0)
FDAAA section 505(o)(3)	181	28 (15.5)	24 (13.3)	129 (71.3)
Accelerated Approval Program	20	10 (50.0)	1 (5.0)	9 (45.0)
Section 506B[c]	76	6 (7.9)	14 (18.4)	56 (73.7)
Study type				
Clinical	165	29 (17.6)	15 (9.1)	121 (73.3)
Nonclinical animal	28	0	5 (17.9)	23 (82.1)
Observational	26	6 (23.1)	2 (7.7)	18 (69.2)
Data submission	54	9 (16.7)	12 (22.2)	33 (61.1)
CMC	9	0	1 (11.1)	8 (88.9)
Other	48	6 (12.5)	7 (14.6)	35 (72.9)

(continued)

Table 1. Timeliness of Completion of Postmarket Requirements (PMRs) and Reportable Postmarket Commitments (PMCs) Instituted for New Drugs Approved by the US Food and Drug Administration (FDA), 2013-2016[a,b] (continued)

	Total No.	No. (%)		
		Early	On time	Late
Study temporality				
New	203	26 (12.8)	21 (10.3)	156 (76.8)
Complete ongoing	25	9 (36.0)	4 (16.0)	12 (48.0)
Submit additional data or final report	53	9 (17.0)	11 (20.8)	33 (62.3)
New analysis on existing data	19	3 (15.8)	4 (21.1)	12 (63.2)
Other	30	3 (10.0)	2 (6.7)	25 (83.3)
Study purpose				
Safety	240	33 (13.8)	34 (14.2)	173 (72.1)
Risk of serious adverse events or toxic effects	81	13 (16.0)	13 (16.0)	55 (67.9)
Long-term clinical safety data	29	11 (37.9)	4 (13.8)	14 (48.3)
Safety or drug toxic effects in a new subpopulation	115	16 (13.9)	14 (12.2)	85 (73.9)
Elderly	3	2 (66.7)	0	1 (33.3)
Renal or hepatic impairment	30	4 (13.3)	8 (26.7)	18 (60.0)
Pregnancy	3	1 (33.3)	0	2 (66.7)
Children	42	5 (11.9)	2 (4.8)	35 (83.3)
Immunocompromised	3	1 (33.3)	0	2 (66.7)
Other, including concomitant drug use	34	3 (8.8)	4 (11.8)	27 (79.4)
Animal studies	28	0	5 (17.9)	23 (82.1)
Assessment of carcinogenic potential	11	0	2 (18.2)	9 (81.8)
Assessment of reproductive toxic effects	1	0	0	1 (100)
General animal safety	16	0	3 (18.8)	13 (81.3)
Efficacy	183	29 (15.8)	26 (14.2)	128 (69.9)
Confirmatory benefit	14	9 (64.3)	1 (7.1)	4 (28.6)
General efficacy	57	6 (10.5)	9 (15.8)	42 (73.7)
Long-term efficacy	9	1 (11.1)	2 (22.2)	6 (66.7)
Efficacy in a new subpopulation	103	13 (12.6)	14 (13.6)	76 (73.8)
Elderly	2	1 (50.0)	0	1 (50.0)
Renal or hepatic impairment	28	4 (14.3)	8 (28.6)	16 (57.1)
Pregnancy	NA	NA	NA	NA
Children	32	4 (12.5)	0	28 (87.5)
Immunocompromised	3	1 (33.3)	0	2 (66.7)
Other, including concomitant drug use	38	3 (7.9)	6 (15.8)	29 (76.3)
Clinical pharmacology	125	15 (12.0)	15 (12.0)	95 (76.0)
CMC	10	0	1 (10.0)	9 (90.0)
Other	21	3 (14.3)	1 (4.8)	17 (81.0)
Expedited pathways				
≥1	237	28 (11.8)	35 (14.8)	174 (73.4)
0	93	22 (23.7)	7 (7.5)	64 (68.8)
Delays				
At least once	68	2 (2.9)	1 (1.5)	65 (95.6)
Never	262	48 (18.3)	41 (15.6)	173 (66.0)

Abbreviations: CMC, chemistry manufacturing and controls; FDAAA, FDA Amendments Act; NA, not applicable; PREA, Pediatric Research Equity Act.

[a] Among 330 PMRs and PMCs expected to be completed by 2020.

[b] Four statutory authorities cover PMRs: FDAAA of 2007 section 505(o)(3) for remaining safety questions, PREA for testing in children, Accelerated Approval Program for confirmatory trials of drugs approved on the basis of poorly characterized surrogate measures, and Animal Rule for drugs approved on the basis of animal data only. One drug was approved during the study period under the Animal Rule, but no quarterly statuses were available for the associated PMR; this PMR, therefore, was excluded from timeliness analyses.

[c] PMCs may be reportable under section 506B of the Food, Drug, and Cosmetic Act by virtue of being agreed to in writing and concerning safety, efficacy, clinical pharmacology, or nonclinical toxicology. Other PMCs are nonreportable, including those regarding chemistry, manufacturing, and production controls; product stability studies; and voluntary studies of the manufacturer's initiative.

completed late by Q4-2020 was 2.00 (IQR, 1.00-4.00) quarters. The PMRs under accelerated approval (median, 10.00 [IQR, 7.00-15.00] quarters) and PREA (median, 12.00 [IQR, 5.25-14.75] quarters) had the longest median projected times

Table 2. Projected vs Actual Time to Completion and Median Lateness for Postmarket Requirements and Reportable Postmarket Commitments Instituted for New Drugs Approved by the US Food and Drug Administration (FDA), 2013-2016

	Median (IQR) quarters [No. of studies]		
	Projected time to completion	Actual time to completion	Lateness
Total	8.00 (3.00-12.00) [282]	10.00 (6.00-14.00) [282]	2.00 (1.00-4.00) [190]
Reporting authority			
PREA	12.00 (5.25-14.75) [38]	13.00 (10.00-17.00) [38]	3.00 (2.00-4.00) [29]
FDAAA section 505(o)(3)	8.00 (3.00-12.00) [161]	10.00 (6.00-14.00) [161]	2.00 (1.00-3.00) [109]
Accelerated Approval Program	10.00 (7.00-15.00) [15]	9.00 (6.00-14.00) [15]	1.50 (1.00-2.00) [4]
Section 506B[a]	5.00 (3.00-11.00) [68]	8.00 (6.00-13.25) [68]	2.00 (1.75-4.00) [48]
Study type			
Clinical	10.00 (5.00-13.00) [133]	11.00 (8.00-17.00) [133]	2.00 (2.00-4.00) [89]
Nonclinical animal	6.00 (3.00-10.00) [28]	7.50 (6.00-12.00) [28]	3.00 (1.00-4.00) [23]
Observational	16.00 (11.00-22.00) [19]	15.00 (13.50-21.50) [19]	3.00 (1.50-3.50) [11]
Data submission	4.00 (3.00-8.00) [52]	6.00 (5.00-10.00) [52]	2.00 (1.00-3.00) [31]
CMC	3.00 (3.00-6.00) [3]	7.00 (7.00-8.50) [3]	3.00 (3.00-3.00) [2]
Other	4.00 (3.00-8.00) [47]	6.00 (5.00-10.00) [47]	2.00 (1.00-3.00) [34]
Study temporality			
New	9.00 (4.25-13.75) [166]	11.00 (7.00-17.00) [166]	2.00 (1.50-4.00) [119]
Complete ongoing	10.00 (4.50-12.00) [23]	9.00 (6.50-13.50) [23]	1.50 (1.00-2.75) [10]
Submit additional data or final report	4.00 (3.00-8.00) [53]	6.00 (5.00-10.00) [53]	2.00 (1.00-3.00) [33]
New analysis on existing data	9.00 (7.50-11.25) [16]	11.00 (10.00-13.25) [16]	2.00 (2.00-3.00) [9]
Other	3.50 (2.00-8.00) [24]	6.00 (5.00-10.00) [24]	2.00 (1.50-3.00) [19]
Study purpose			
Safety	8.00 (4.00-13.00) [206]	10.00 (6.00-15.00) [206]	2.00 (1.00-4.00) [139]
Efficacy	8.00 (3.75-12.00) [152]	10.00 (6.00-14.00) [152]	2.00 (1.00-4.00) [97]
Clinical pharmacology	8.00 (4.00-12.00) [104]	10.00 (6.00-14.00) [104]	2.00 (1.25-5.00) [74]
CMC	6.00 (3.00-9.50) [4]	8.50 (7.00-12.00) [4]	3.00 (3.00-4.50) [3]
Other	4.00 (2.00-8.00) [21]	6.00 (5.00-10.00) [21]	2.00 (1.00-3.00) [17]
Expedited pathways			
≥1	8.00 (3.00-12.00) [205]	10.00 (6.00-14.00) [205]	2.00 (1.00-3.00) [142]
0	8.00 (4.00-13.00) [77]	10.00 (6.00-17.00) [77]	3.00 (2.00-4.00) [48]
Delays			
At least once	8.00 (5.50-12.00) [39]	14.00 (10.00-20.00) [39]	5.00 (3.00-6.25) [36]
Never	7.00 (3.00-12.00) [243]	9.00 (6.00-14.00) [243]	2.00 (1.00-3.00) [154]

Abbreviations: CMC, chemistry manufacturing and controls; FDAAA, FDA Amendments Act; PREA, Pediatric Research Equity Act.

[a] Of the Food, Drug, and Cosmetic Act.

to completion. The PREA studies had the highest median lateness (3.00 [IQR, 2.00-4.00] quarters), and accelerated approval had the lowest (1.50 [IQR, 1.00-2.00] quarters).

Discussion | Among PMRs and PMCs issued to new FDA-approved drugs between 2013 and 2016, approximately three-quarters of those due by 2020 were not submitted on time. Frequency and degree of lateness varied by reporting authority and study characteristics. Our results are not generalizable to supplemental indications, approvals after 2016, and nonreportable PMCs.

Delays in delivering needed postapproval safety and efficacy information for novel drugs have implications for patient care,[6] particularly for unresolved clinical questions and populations excluded from preapproval trials. To address this problem, Congress should consider providing the FDA with more authority, such as the ability to institute automatic civil monetary penalties when pharmaceutical manufacturers do not fulfill their requirements and commitments on time.

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