Supplementary Content

US Food and Drug Administration utilization of postmarketing requirements and postmarketing commitments, 2009-2018

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eTable 1. US Food and Drug Administration authorities for the issuance of postmarketing requirements and commitments.[1–5]

Type	Authority	Year implemented	Requirement or commitment purpose
PMR	Accelerated approval pathway	1992	Confirmatory studies to describe and verify clinical benefit.
	Animal efficacy rule	2002	Demonstrate safety and efficacy at the time of therapeutic use.
	Pediatric Research Equity Act	2003	Pediatric studies and clinical trials to improve pediatric-specific therapeutic labeling.
	Food and Drug Administration Amendments Act, section 505(o)	2007 (*effective 2008*)	Assess known serious risk or signals of serious risk or identify unexpected serious risk for approved therapeutics.
PMC	Food, Drug, and Cosmetic Act, section 506B	1997[a]	Studies agreed upon by sponsors and FDA with annual reporting mandated for sponsors.
	"Non-506B" postmarketing commitments	1997[b]	Studies agreed upon by sponsors and FDA that are not subject to reporting requirements.

PMR: postmarketing requirement; PMC: postmarketing commitment.

[a] Although provisions for agreed upon postapproval study commitments were outlined in 1997, the term "postmarketing commitment" was used prior to 2008 to describe all postapproval studies required by FDA, agreed upon by sponsors and FDA, and voluntarily conducted by sponsors.

[b] "Authority" created by exclusion of certain postmarketing commitments from Food, Drug, and Cosmetic Act, section 506B.

eBox. Categorization of postmarketing requirements and commitments by type of study outlined.[2]
A. New prospective cohort studies, registries, and clinical trials New randomized controlled trials or other clinical trials evaluating safety and efficacy; prospective cohort studies and registries.[a]
B. Complete or submit results from ongoing prospective cohort studies, registries, and clinical trials Instead of requesting a new prospective study or trial, completion and submission of the results from ongoing prospective cohort studies or trials.
C. New retrospective observational studies New case-control, cross sectional, and retrospective cohort studies; analyses of spontaneous adverse event reporting data.
D. Animal or "other" studies required New animal trials; pharmacokinetic or pharmacodynamics trials; in vitro or in vivo, drug transport, drug-drug or drug-therapeutic, prenatal and postnatal development, antidrug antibody response, mass balance, dosing, lactation, or QT/QTc studies.
E. Analyze/follow-up from observational studies, registries, or clinical trials (and other flexible requirements) Longer follow-up or new analyses of data from existing trials or studies; submission of a final report for ongoing case-control, cross sectional, or retrospective cohort studies; studies or trials that can be done as expansions of the previous observational studies; enrollment of additional patients in an existing registry; "flexible" requirements.[b]
[a] Generally includes "controlled clinical investigation(s), other than phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of this Act."[6] Under section 801 of the FDA Amendments Act, only applicable clinical trials are required to submit information to ClinicalTrials.gov. Trials that must be registered "either were initiated after September 27, 2007, or initiated on or before that date and were still ongoing as of December 26, 2007," and meet one of three conditions: have one or more sites in the USA, is conducted under an FDA investigational new drug application, or involves a drug or biologic that is manufactured in the USA or its territories and is exported for research.[6] We did not classify trials that only evaluated pharmacokinetics under the first two categories, but did include trials evaluating pharmacokinetics as well as safety, if those trials enrolled patients rather than healthy volunteers. [b] Some postmarketing requirements and postmarketing commitments can be satisfied in more than one way; for example, those that outline that drug manufacturers have the option of collecting safety data from an open label extension of a clinical trial that the manufacturer has already committed to perform, from separate longer term, open label safety trials, or from long term controlled safety and efficacy trials.

eAppendix. Additional methods pertaining to the classification of indications investigated by clinical postmarketing requirements and commitments.

Overview of abstraction approach for indications investigated by clinical postmarketing requirements and postmarketing commitments

We relied exclusively on postmarketing requirement and commitment descriptions provided in original FDA approval letters when that information was adequate to abstract indication, study design, and purpose. When a postmarketing requirement or commitment description referenced an identifier for an ongoing clinical study (e.g., a National Clinical Trial number assigned by ClinicalTrials.gov, a study identification provided by sponsors, or the full title of a clinical trial), then the ClinicalTrials.gov registration corresponding to that study was located and used to supplement the postmarketing requirement or commitment description for abstraction.

If there was any ambiguity in the described indication for a postmarketing requirement or commitment (e.g., if the drug was approved for second-line use, but a postmarketing requirement did not specify whether patients should have received previous treatment), we attempted to identify a corresponding trial registration on ClinicalTrials.gov, using a previously described approach.[2] If a corresponding registration was identified, it was used in conjunction with the original FDA description to classify the postmarketing requirement or commitment.

The use of the "unclear indication" designation was reserved for ambiguous postmarketing requirement and commitment indications for which no corresponding trial was found, as well as patient exposure registries that did not restrict enrollment. In some cases, it was possible to identify a clinical or demographic subgroup despite ambiguity about the investigated indication (e.g. pregnancy registries), which was then recorded.

If a postmarketing requirement or commitment was determined to investigate both an original and a new or modified indication (e.g., by outlining a clinical study enrolling patients with multiple potential subtypes of non-Hodgkin lymphoma, when the therapeutic was originally approved for only one of the eligible subtypes), then it was classified as investigating the modified or new indication, due to that postmarketing requirement or commitment potentially generating evidence for therapeutic use in expanded disease populations or new diseases beyond the scope of the original approved indication.

Of note, postmarketing requirements describing pediatric studies of therapeutics for the treatment of original indicated diseases were classified as "original indication: demographic subgroup" regardless of whether therapeutics were originally indicated for pediatric use. Therapeutics not receiving orphan drug designation and treating diseases that occur in pediatric populations may be approved for use in adults prior to completion of pediatric studies, with completion of those studies subsequently outlined as postmarketing requirements issued under the Pediatric Research Equity Act.[7] For the purpose of classifying postmarketing requirement indications, all pediatric studies of original approved diseases were considered outstanding investigations of the original approved therapeutic indication, in the pediatric demographic subgroup. Postmarketing requirements describing pediatric studies investigating therapeutic uses for expanded disease populations (e.g., based on clinical characteristics) or new diseases were classified as "modified indication" or "new indication," respectively.

Example abstractions of indications investigated by clinical postmarketing requirements (PMRs) and postmarketing commitments (PMCs) outlined in original FDA approval letters for new therapeutics.[8]

Therapeutic: Erenumab-aooe (Aimovig)

Approved indication: Preventative treatment of migraine.

PMR: PMR 3392-2 An open-label pharmacokinetic, safety, and tolerability study in pediatric migraine patients ages 6 through 11 years.

National Clinical Trial number (NCT): Not used for abstraction, due to information available in PMR.

PMR indication: Original indication: Demographic subgroup (*pediatric patients ages 6 through 11 years*).

Therapeutic: Baloxavir marboxil (Xofluza)

Approved indication: Acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

PMC: 3503-6 Conduct a randomized, double-blind, controlled clinical trial evaluating efficacy and safety of baloxavir marboxil in subjects hospitalized with severe influenza.

NCT: Not used for abstraction, due to information available in PMC.

PMC indication: Modified indication (*severe influenza*).

Therapeutic: Lorlatinib (Lorbrena)

Approved indication: Patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on: crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease.

PMR: 3500-1 Conduct and submit the results of at least one multicenter, randomized clinical trial that verifies and describes the clinical benefit of lorlatinib in patients with locally advanced or metastatic non-small cell lung cancer without a history of prior systemic therapy for advanced disease and whose tumors harbor anaplastic lymphoma kinase (ALK) gene arrangement.

NCT: Not used for abstraction, due to information available in PMR.

PMR indication: Modified indication (*due to inclusion of patients, including those with locally advanced disease, without history of systemic therapy*).

Therapeutic: Tedizolid phosphate (Sivextro)

Approved indication: Acute bacterial skin and skin structure infections (ABSSSI).

PMR: 2159-3: Conduct an open-Label, Multicenter Study of 10-14 days IV SIVEXTRO (tedizolid phosphate) for hospital-acquired late onset sepsis in full term and preterm neonates and infants aged 5 days to <3 months.

NCT: Not used for abstraction, due to information available in PMR.

PMR indication: New indication (*hospital-acquired late onset neonatal sepsis*).

Therapeutic: Sacubitril; Valsartan (Entresto)

Approved indication: Reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.

PMR: 2924-2 A multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by comprehensive neurocognitive battery and PET imaging in patients with chronic heart failure with preserved ejection fraction.

NCT: Not used for abstraction, due to information available in PMR.

PMR indication: New indication (*Preservation of cognitive function in patients with chronic heart failure with preserved ejection fraction*).

Therapeutic: Valbenazine tosylate (Ingrezza)

Approved indication: Tardive dyskinesia.

PMC: 3177-5 Perform a randomized controlled trial to assess whether a higher dose would confer additional therapeutic benefit.

NCT: Not identified.

PMC indication: Original indication: General population.

Therapeutic: Ribociclib succinate (Kisqali)

Approved indication: In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

PMR: 3168-1 Conduct a clinical trial to assess the efficacy and safety of an alternative dosing regimen for ribociclib.

NCT: NCT03822468 (*enrolls treatment-naïve pre- or postmenopausal patients with advanced or metastatic, ER+, HER2- breast cancer*).

PMR indication: Modified indication (*due to inclusion of premenopausal patients*).

Therapeutic: Dasabuvir sodium; Ombitasvir; Paritaprevir; Ritonavir (Viekira Pak)

Approved indication: Chronic Hepatitis C (HCV) Genotype (GT) 1 infection.

PMC: 2830-11 Submit the final report and datasets for the Phase 3 clinical trial M13-961 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

NCT: NCT01767116 (*enrolls treatment-naïve adults with chronic HCV GT 1b infection*).

PMC indication: Original indication: Clinical subgroup (*treatment-naïve patients with chronic HCV GT 1b infection*).

Therapeutic: Pimavanserin tartrate (Nuplazid)

Approved indication: Hallucinations and delusions associated with Parkinson's disease psychosis.

PMC: 3069-2 Conduct a randomized placebo-controlled trial or trials with predominantly frail and elderly subjects that would involve exposure of at least 500 subjects to pimavanserin 34 mg daily for a minimum of 8 weeks.

NCT: NCT03575052 (*enrolls patients with neuropsychiatric symptoms resulting from "neurodegenerative disease" including Parkinson's disease, Alzheimer's disease, vascular dementia, etc.*).

PMC indication: New indication (*patients with neurodegenerative diseases other than Parkinson's disease*).

Therapeutic: Idelalisib (Zydelig)

Approved indication: Relapsed chronic lymphocytic leukemia, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies; relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies.

PMR: PMR 2180-6 Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in patients with previously treated indolent non-Hodgkin lymphomas.

NCT: NCT01732913 (*enrolls patients with previously treated indolent non-Hodgkin lymphomas, including follicular lymphoma, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia, and marginal zone lymphoma*).

PMR indication: New indication (*non-Hodgkin lymphomas other than follicular and small lymphocytic lymphomas*).

eTable 2. Excluded new diagnostic agents receiving original Food and Drug Administration approval, 2009-2018.[a]

Diagnostic agent	Approval year	Indication
Ioflupane I-123	2011	Evaluation of adult patients with suspected Parkinsonian syndromes (PS).
Gadobutrol	2011	Detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system.
Citric acid; Magnesium oxide; Sodium picosulfate	2012	Cleansing of the colon as a preparation for colonoscopy.
Choline C-11	2012	Positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging (MRI).
Florbetapir F-18	2012	Estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.
Flutemetamol F-18	2013	Estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.
Gadoterate meglumine	2013	Detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.
Technetium TC-99M tilmanocept	2013	Assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma.
Sulfur hexafluoride lipid-type A microspheres	2014	Opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Florbetaben F-18	2014	Estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline.
Fluciclovine F-18	2016	Positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.
Gallium dotatate Ga-68	2016	Localization of somatostatin receptor positive neuroendocrine tumors (NETs).
Macimorelin acetate	2017	Diagnosis of adult growth hormone deficiency (AGHD).

[a] Among 356 products designated as "New Molecular Entities" by FDA from 2009 to 2018, 13 (3.7%) were agents indicated for the diagnosis rather than the treatment of disease (e.g., contrast agents or bowel preparatory agents), and were excluded from analyses.

eTable 3. Categorization of postmarketing requirements and commitments for new therapeutics receiving original Food and Drug Administration approval, 2009-2018, by issuing authority.

PMR/PMC study description		PMRs/PMCs, No. (%)	PMR authority, No. (%)				PMC authority[a], No. (%)	
			FDAAA	PREA	AA	AER	506B	Non-506B
Total		1978	801	257	62	3	273	582
Clinical PMRs and PMCs	Total	750 (37.9)	331 (41.3)	207 (80.5)	59 (95.2)	3 (100.0)	141 (51.6)	9 (1.5)
	New prospective cohort study, registry, or clinical trial	448 (22.6)	169 (21.1)	191 (74.3)	31 (50.0)	3 (100.0)	48 (17.6)	6 (1.0)
	Complete or submit results from prospective cohort study, registry, or clinical trial	125 (6.3)	40 (5.0)	1 (0.4)	21 (33.9)	0 (0)	62 (22.7)	1 (0.2)
	New retrospective observational study	33 (1.7)	33 (4.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	New analysis or follow-up for cohort study, registry, or clinical trial, or "flexible" requirements[b]	144 (7.3)	89 (11.1)	15 (5.8)	7 (11.3)	0 (0)	31 (11.4)	2 (0.3)
Nonclinical PMRs and PMCs	New or follow-up of animal or "other" study	1228 (62.1)	470 (58.7)	50 (19.5)	3 (4.8)	0 (0)	132 (48.4)	573 (98.5)

PMR: postmarketing requirement; PMC: postmarketing commitment; FDAAA: Food and Drug Administration Amendments Act; PREA: Pediatric Research Equity Act; AA: Accelerated Approval; AER: Animal Efficacy Rule.

[a] "506B" refers to postmarketing commitments subject to reporting requirements under section 506B of the Federal Food, Drug, and Cosmetic Act. Postmarketing commitments not subject to this rule are denoted as "Non-506B."

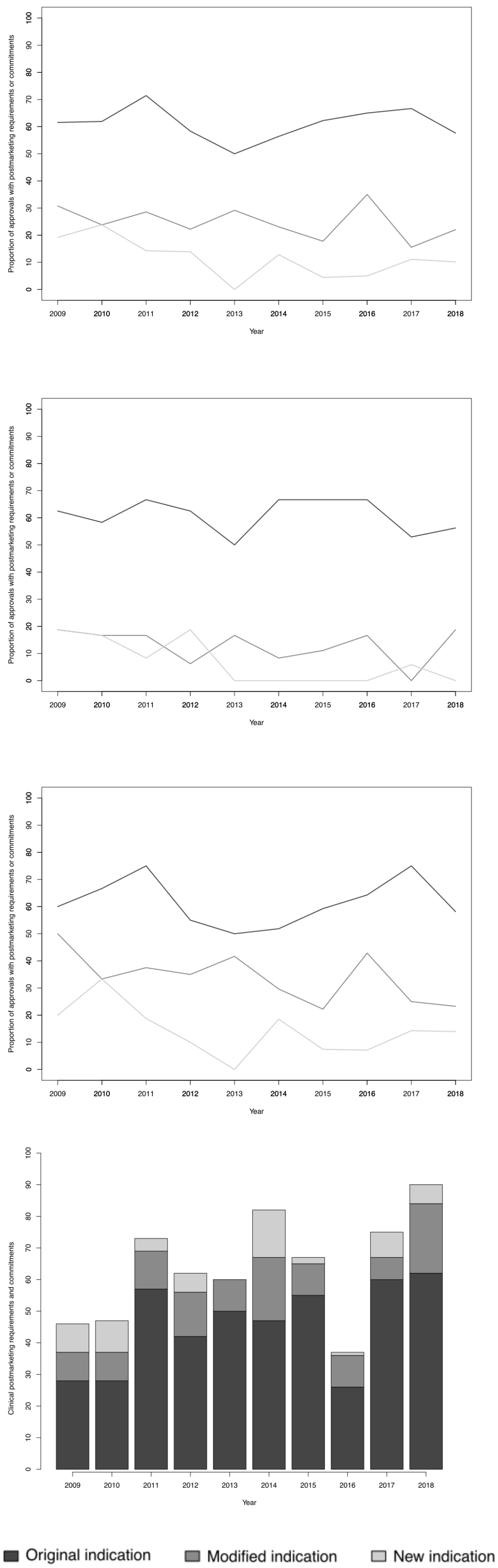
[b] "Flexible" requirements include those that can be fulfilled by expansion of previous studies, multiple study designs (e.g., by a new prospective cohort study or a case-control study), and other new analyses of clinical data.

[c] "Other" studies include pharmacokinetic/pharmacodynamic trials; drug transport, drug-drug or drug-therapeutic studies; mass balance studies; manufacturing studies; and other nonclinical analyses.

eTable 4. Clinical postmarketing requirements and commitments for new therapeutics receiving original Food and Drug Administration approval, 2009-2018, by therapeutic area.

Therapeutic area	Therapeutics, No. (%)	Clinical PMRs and PMCs, median (IQR)	Clinical PMRs and PMCs, No. (%)	New prospective cohort study, registry, or clinical trial, No. (%)	Complete or submit results from prospective cohort study, registry, or clinical trial, No. (%)	New retrospective observational study, No. (%)	New analysis or follow-up for cohort study, registry, or clinical trial, or "flexible" requirements, No. (%)
Total	343	2 (1-3)	750	448	125	33	144
Autoimmune, musculoskeletal, and dermatology	39 (11.4)	2 (1-4)	110 (14.7)	75 (16.7)	12 (9.6)	7 (21.2)	16 (11.1)
Cancer and hematology	97 (28.3)	2 (1-3)	190 (25.3)	71 (15.8)	59 (47.2)	2 (6.1)	58 (40.3)
Cardiovascular and diabetes	40 (11.7)	2 (0.75-3)	79 (10.5)	55 (12.3)	2 (1.6)	17 (51.5)	5 (3.5)
Gastrointestinal and metabolism	31 (9.0)	2 (1-3)	72 (9.6)	39 (8.7)	2 (1.6)	1 (3.0)	30 (20.8)
Infectious disease	55 (16.0)	2 (1-4)	160 (21.3)	99 (22.1)	47 (37.6)	1 (3.0)	13 (9.0)
Neurology and psychiatry	34 (9.9)	2.5 (1-4)	94 (12.5)	79 (17.6)	0 (0)	0 (0)	15 (10.4)
Other	47 (13.7)	0 (0-1)	45 (6.0)	30 (6.7)	3 (2.4)	5 (15.2)	7 (4.9)

PMR: postmarketing requirement; PMC: postmarketing commitment; IQR: interquartile range.


Proportion of approvals with postmarketing requirements or commitments
Year
Proportion of approvals with postmarketing requirements or commitments
Year
Proportion of approvals with postmarketing requirements or commitments
Year
Clinical postmarketing requirements and commitments
Year
Original indication
Modified indication
New indication

eFigure 1: Indications of postmarketing requirements and commitments outlined for therapeutics receiving original Food and Drug Administration approval, 2009-2018. (a) Proportion of 343 therapeutics with at least one postmarketing requirement or commitment investigating original, modified, and new indications. (b) Proportion of 137 therapeutics with no expedited review designations, and with at least one postmarketing requirement or commitment investigating original, modified, and new indications. (c) Proportion of 206 therapeutics with any expedited review designations, and with at least one postmarketing requirement or commitment investigating original, modified, and new indications. (d) Number of postmarketing requirements and commitments, 2009-2018, by study indication. Note: "Expedited review designations" refers to the following US Food and Drug Administration expedited review program designations: priority review, accelerated approval, fast track, and/or breakthrough therapy.

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Title:	U.S. Food and Drug Administration utilization of postmarketing requirements and postmarketing commitments, 2009-2018
Manuscript ID:	CT-20-0326.R2
Funding Information:	There are no funders to report for this submission
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Running Head:	Postmarketing requirements and commitments
Keywords:	The US Food and Drug Administration *, Pharmaceutical regulation *, Postmarketing requirements *, Postmarketing commitments *, Clinical trials *, Clinical evidence *