

Original Investigation

Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012

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IMPORTANCE Some new drug applications fail because of inadequate drug performance and others are not approved because the information submitted to the US Food and Drug Administration (FDA) is unsatisfactory to make that determination. Resubmission of failed applications is costly, delaying marketing approval and the availability of new drugs to patients.

OBJECTIVE To identify the reasons that FDA marketing approval for new drugs was delayed or denied.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review of FDA documents and extraction of data were performed. We examined all drug applications first submitted to the FDA between 2000 and 2012 for new molecular entities (NMEs), which are active ingredients never before marketed in the United States in any form. Using FDA correspondence and reviews, we investigated the reasons NMEs failed to obtain FDA approval.

MAIN OUTCOMES AND MEASURES Reasons for delayed FDA approval or nonapproval of NME applications.

RESULTS Of the 302 identified NME applications, 151 (50%) were approved when first submitted and 222 (73.5%) were ultimately approved. Seventy-one applications required 1 or more resubmissions before approval, with a median delay to approval of 435 days following the first unsuccessful submission. Of the unsuccessful first-time applications, 24 (15.9%) included uncertainties related to dose selection, 20 (13.2%) choice of study end points that failed to adequately reflect a clinically meaningful effect, 20 (13.2%) inconsistent results when different end points were tested, 17 (11.3%) inconsistent results when different trials or study sites were compared, and 20 (13.2%) poor efficacy when compared with the standard of care. The frequency of safety deficiencies was similar among never-approved drugs compared with those with delayed approval (43 of 80 never approved [53.8%] vs 37 of 71 eventually approved [52.1%]; difference, 1.7% [95% CI, -14.86% to 18.05%]; $P = .87$). However, efficacy deficiencies were significantly more frequent among the never-approved drugs than among those with delayed approvals (61 of 80 never approved [76.3%] vs 28 of 71 eventually approved [39.4%]; difference, 36.9% [95% CI, 20.25% to 50.86%]; $P < .001$).

CONCLUSIONS AND RELEVANCE Several potentially preventable deficiencies, including failure to select optimal drug doses and suitable study end points, accounted for significant delays in the approval of new drugs. Understanding the reasons for previous failures is helpful to improve the efficiency of clinical development for new drugs.

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The road from medical product discovery to marketing is typically long and costly. The interval between initial clinical testing and product approval has been estimated to average 8 years¹ and only 1 in 6 drugs entering clinical trials ultimately obtains US Food and Drug Administration (FDA) approval.² To obtain marketing approval for new drugs, developers must provide substantial evidence of safety and efficacy for the proposed indication.³ In a number of failed applications, deficiencies are successfully addressed in resubmissions resulting in delayed approval, whereas others are never approved for marketing. Nonapproval of drugs is critical to prevent the marketing of ineffective or harmful products. However, many drugs are not approved not because they are unsafe or ineffective, but because the information is unsatisfactory to make that determination. Delays and failures that occur late in development affect the availability of innovative new drugs and increase the costs of drug development.⁴ To avoid preventable late-stage deficiencies in drug development and their negative consequences, it is important to understand the nature of these deficiencies.

We reviewed marketing applications for new molecular entities (NMEs) submitted to the FDA to characterize the scientific and regulatory reasons approval was delayed or denied.

Methods

We examined all marketing applications for therapeutic NMEs that were submitted to the Center for Drug Evaluation and Research (CDER) for the first time between October 1, 2000, and September 30, 2012. This does not represent all drug applications to the FDA and does not include generic drugs, supplementary drug applications, and biologic applications.

Multiple applications for the same NME in various dosage forms (eg, tablet, suspension, injectable) and multiple applications for different indications were only evaluated once. Nontherapeutic diagnostic products, such as radiocontrast agents, and drug applications withdrawn by sponsors before FDA action was taken were excluded.

All new drug applications not approved when first submitted to the FDA were considered failures. We extracted information from FDA action letters (the FDA's official responses to failed applications) and both internal and publicly available reviews and correspondence that describe deficiencies identified by the FDA. Publicly available information on failed and approved drugs is posted on the FDA's website⁵ and in transcripts of advisory committee meetings.⁶

We grouped the deficiencies into 4 primary categories: (1) efficacy; (2) safety; (3) chemistry, manufacturing, and controls (CMC); and (4) product labeling. These categories are individually addressed in new drug applications and in FDA reviews and action letters, providing a logical framework for the analysis of deficiencies. Efficacy deficiencies referred to those for which the intended effect of the drug was not satisfactorily demonstrated, or the nature or size of the intended effect was not satisfactory to allow drug approval. Safety deficiencies referred to those for which the characterization of the risk of adverse events or the nature

and severity of observed adverse events was not satisfactory to allow drug approval. Within each of these categories, we documented the more detailed reasons that either safety or efficacy was not satisfactorily demonstrated. Chemistry, manufacturing, and control deficiencies were those for which adequate physical quality of the drug product was not ensured. Labeling deficiencies were those for which the product labeling failed to adequately represent the information needed to market the drug to consumers.

We defined *uncertainty or disagreement on dose* as inability to determine a suitable dose for drug labeling. This was generally the result of inadequate dose exploration and included applications with inadequate safety or efficacy data for the proposed dose, conflicting efficacy or safety data when the same dose was used in different studies, and dose-related toxic effects for which a lower dose appeared potentially effective. Unlike deficiencies such as unsatisfactory end point, which we categorized primarily as a deficiency in demonstrating efficacy rather than safety, dosing uncertainty inevitably affected the evaluation of both the safety and efficacy of the drug. Hence uncertainty or disagreement on dose was treated as both a safety and an efficacy deficiency.

We recorded all deficiencies cited in the action letter for all dosage forms of the drug that had any potential role in the regulatory decision, omitting minor deficiencies (such as packaging problems, remediable manufacturing specifications, and nonserious clinical concerns) frequently addressed after approval. The decision to include a deficiency in the analysis was made by consensus of the review team based on the statements in the action letter.

Many drugs not approved following initial submission (first-cycle failures) were resubmitted by sponsors after addressing deficiencies. We compared the deficiencies in applications that eventually were approved by June 30, 2013 (delayed approvals), with those in applications that were not approved during the period of our study (never approved) to identify those that were corrected after a failed application and that might possibly have been prevented if they were identified earlier.

We compared the approval rates for drugs granted priority review with those that were given a standard review. Applications qualified for priority-review status if the new drug treated a serious condition and appeared to provide significant improvements in safety or effectiveness compared with available therapies.⁷

We used descriptive statistics to represent approval rates and frequencies of specific deficiencies. The Fischer exact test (SAS Institute Inc, version 9.3) was used to compare differences in the frequency of deficiencies. We regarded 2-sided *P* values less than .05 as statistically significant.

Results

New drug applications for 332 NMEs were filed with CDER during the 12 years between October 1, 2000, and September 30, 2012. Twenty-three applications for nontherapeutic drugs (eg, radiocontrast agents) and 7 applications withdrawn by spon-

Figure. Flow Diagram of Outcomes for New Molecular Entities Submissions to the Center for Drug Evaluation and Research of the US Food and Drug Administration Between 2000 and 2012

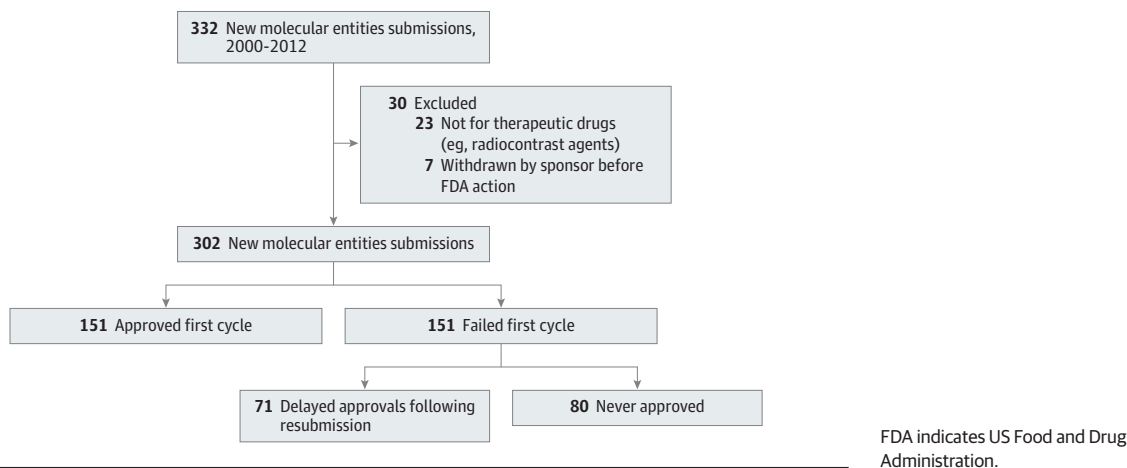


Table 1. First-Cycle Approval Rates by Medical Specialty

Medical Specialty	Total NMEs Submitted	Approved During First Review Cycle, No. (%)
Oncology	61	44 (72)
Metabolic diseases ^a	45	21 (47)
Neurology/psychiatry	42	14 (33)
Infectious diseases	39	23 (59)
Cardiology	22	7 (32)
Ophthalmology	15	7 (47)
Pulmonology/allergy	13	4 (31)
Gastroenterology	13	9 (69)
Urology	11	4 (36)
Reproductive medicine	10	4 (40)
Dermatology	9	3 (33)
Rheumatology/analgesia	7	3 (43)
Hematology/hemostasis	7	4 (57)
Other	8	4 (50)

Abbreviation: NMEs, new molecular entities.

^a Includes diabetes mellitus, hyperlipidemia, iron overload, hyponatremia, osteoporosis, menopausal symptoms, hyperuricemia, obesity, and Gaucher disease.

sors prior to an FDA action were excluded. Of the remaining 302 NMEs, 151 (50%) were approved after the first review cycle (Figure).

First-cycle approval rates were 72 of 106 (67.9%) for applications granted a priority review and 79 of 196 (40.3%) for drugs given a standard review.

Approval rates varied for each medical specialty (Table 1) ranging from 72% for oncology drugs to 31% for pulmonology and allergy drugs.

Eighty-seven of 151 first-cycle failures (57.6%) were resubmitted for the same indications prior to June 30, 2013. Of these, 55 applications (63.2%) were approved during a second review cycle, 13 (14.9%) during a third review cycle, and 3 (3.4%) during further review cycles. Of the 151 first-cycle failures, 71 (47.0%) eventually obtained approval in a median of 435 days

following the first action letter (range, 47-2374 days). Overall, of the 302 drugs evaluated, 222 (73.5%) eventually achieved marketing approval during the study. These approved drugs are listed in eTable 1 in the Supplement.

Reasons Drug Applications Failed

Failures in Dose Selection

Uncertainty about the optimal dose to maximize efficacy and to minimize safety risks occurred in 24 first-cycle failures (15.9%). Most of the drugs for which the FDA recommended exploring other doses were intended to treat chronic diseases, such as seizure disorders (3 drugs), pain and inflammation (2 drugs), asthma (2 drugs), hypertension (1 drug), and angina (1 drug). An antimicrobial drug and a drug to treat acute hemorrhage were the only 2 exceptions.

Efficacy

The reasons for which products failed to demonstrate efficacy are shown in Table 2. Twelve examples of deficiencies described in FDA action letters and the links to those action letters and reviews can be accessed in eTable 2 in the Supplement.

Eleven drugs (7.3%) failed because the populations that were studied did not reflect the populations likely to use the drug.

Twenty drugs (13.2%) failed because end points used in clinical trials were unsatisfactory for approval. Unsatisfactory end points included those for which the nature of the end point or the time when the end point was measured failed to capture a meaningful clinical benefit. Examples included measurement of outcome at a time point too early to demonstrate the full treatment effect, discordance between FDA reviewers and primary investigators regarding interpretation of a successful treatment outcome, cancer trials showing efficacy on an end point of progression-free survival but not overall survival, and trials with an end point of change in a pathological measurement (eg, forced vital capacity, uric acid), in which the size of the change was not known to correlate with clinical benefit.

Table 2. Deficiencies in the Demonstration of Efficacy During First-Cycle Review^a

	Efficacy Deficiencies, No. (%)		
	First-Cycle Review Failures (n = 151)	Delayed Approvals Following Resubmission (n = 71)	Drugs Never Approved During Study (n = 80)
Population			
Population not appropriate to reflect intended use	11 (7.3)	3 (4.2)	8 (10.0)
Size of population too small to demonstrate efficacy	4 (2.6)	0	4 (5.0)
Intervention			
Uncertainty/disagreement about appropriate dose	24 (15.9)	9 (12.7)	15 (18.8)
Inability to define noninferiority margin ^b	9 (6)	3 (4.2)	6 (7.5)
Confounding by concomitant medication	8 (5.3)	2 (2.8)	6 (7.5)
End point			
Unsatisfactory	20 (13.2)	5 (7.0)	15 (18.8)
Study conduct			
Missing data	3 (2.0)	0	3 (3.8)
Data integrity	8 (5.3)	4 (5.6)	4 (5.2)
Study outcome			
Inconsistent results for multiple end points	20 (13.2)	6 (8.5)	14 (17.5)
Inconsistent results in different trials or at different study sites	17 (11.3)	3 (4.2)	14 (17.5)
Inadequate efficacy compared with standard of care	20 (13.2)	7 (9.9)	13 (16.3)

^a Multiple kinds of deficiencies were possible for each application.

^b The noninferiority margin is determined based on the effect size of the approved comparator drug and the maximum decrement in efficacy compared with the comparator that is judged to be medically acceptable.⁸

Table 3. Number of Drugs With Significant Adverse Events Occurring in Clinical Trials

Type of Adverse Event	No. (%) ^a		
	First-Cycle Review Failures (n = 151)	Delayed Approvals Following Resubmission (n = 71)	Drugs Never Approved During Study (n = 80)
Cardiovascular ^b	14 (9.3)	3 (4.2)	11 (13.8)
Overall mortality ^c	11 (7.3)	0	11 (13.8)
Hepatic	9 (5.9)	2 (2.8)	7 (8.8)
Neuropsychiatric	9 (5.9)	3 (4.2)	6 (7.5)
Hemostasis	6 (4.0)	1 (1.4)	5 (6.3)
Gastrointestinal	5 (3.3)	2 (2.8)	3 (3.8)
Drug interactions	4 (2.6)	0	4 (5.0)
Infections	4 (2.6)	3 (4.2)	1 (1.3)
Allergy/immunology	4 (2.6)	1 (1.4)	3 (3.8)
Neoplasm	4 (2.6)	2 (2.8)	2 (2.5)
Renal	3 (2.0)	3 (4.2)	0
Musculoskeletal	2 (1.3)	2 (2.8)	0

^a Not every failed application had a significant adverse event. See Tables 2, 4, and 5 for other deficiencies.

^b Included proarrhythmic activity; effects on myocardial function; and thromboembolic events affecting the coronary, cerebral, and peripheral vasculature.

^c All-cause mortality was higher in the investigational group of the study than in the comparator group.

Twenty drugs (13.2%) failed because inconsistent results for multiple predefined end points in clinical studies prevented approval. Inconsistencies in efficacy for portions of the study population prevented approval for 17 drugs (11.3%). In these cases, efficacy was typically only seen in some studies or study sites and not in others or only in subpopulations that were not part of the original analytic plan.

There were 20 drugs (13.2%) that despite showing superiority to placebo were considered to have inadequate efficacy compared with the standard of care. Examples included drugs targeting serious indications (eg, treatment

of arrhythmias, cancer palliation, and schizophrenia) for which more effective approved products already existed and trials did not show other advantages (eg, improved safety or value as salvage therapy).

Safety

Most commonly, safety concerns were the result of adverse events observed in clinical trials (Table 3) that were serious enough to have a significant effect on patient health (eg, drug-related stroke, myocardial infarction, hepatitis, renal failure, suicidal ideation, and bleeding).

Table 4. Number of Drugs With Safety Deficiencies Other Than Clinically Observed Adverse Events

	No. (%) ^a		
	First-Cycle Review Failures (n = 151)	Delayed Approvals Following Resubmission (n = 71)	Drugs Never Approved During Study (n = 80)
Safety studies not done or inadequate			
QT prolongation studies	7 (4.6)	5 (7.0)	2 (2.5)
CYP enzyme studies	3 (2.0)	2 (2.8)	1 (1.3)
Carcinogenicity studies	3 (2.0)	2 (2.8)	1 (1.3)
Reproductive toxicology studies	1 (0.7)	0	1 (1.3)
Potential risks based on animal toxicology (eg, carcinogenicity)	8 (5.3)	4 (5.6)	4 (1.3)
Theoretical risks related to drug mechanism of action, structure, or class	11 (7.3)	7 (9.9)	4 (5.0)
Potential risks to untested study populations			
Population too small to characterize drug safety	2 (1.3)	1 (1.4)	1 (1.3)
Safety population inadequate for proposed dose/duration of therapy	5 (3.3)	4 (5.6)	1 (1.3)
Population inadequate to address safety in patients with renal/hepatic impairment	7 (4.6)	4 (5.6)	3 (3.8)
Dose selection	24 (15.9)	9 (12.7)	15 (18.8)

Abbreviation: CYP, cytochrome P.
^a Not every failed application had a significant adverse event. See Tables 2, 4, and 5 for other deficiencies.

Table 5. Frequency of Safety, Efficacy, CMC, and Labeling Deficiencies for Drugs Failing First-Cycle Review

Type of Deficiency	First-Cycle Review Failures (n = 151)	Delayed Approvals Following Resubmission (n = 71)	Drugs Never Approved During Study (n = 80)	P Value
Efficacy deficiencies only	48 (31.8)	15 (21.1)	33 (41.3)	.01
Safety and efficacy deficiencies	41 (27.2)	13 (18.3)	28 (35.0)	.03
Safety deficiencies only	39 (25.8)	24 (33.8)	15 (18.8)	.04
CMC alone	17 (11.3)	13 (18.3)	4 (5.0)	.02
Labeling alone	4 (2.6)	4 (5.6)	0	.05
CMC and labeling	2 (1.3)	2 (2.8)	0	.22

Abbreviation: CMC, chemistry, manufacturing, and controls.

For 11 drugs that failed to gain approval on initial review, mortality rates in clinical trials were numerically higher in patients treated with the new drug than in patients treated with comparator drugs. None were subsequently approved during the study period. Other safety concerns delaying or preventing drug approval included missing or inadequate clinical or nonclinical studies that are usually included in new drug applications. In several applications, study populations were either too small or inadequate to characterize risks anticipated during clinical use. In others, theoretical risks raised by signals in animal studies or by the structure or mechanism of action of the drug were not addressed. Concerns about dose selection were also frequently identified (Table 4).

Labeling and Chemistry, Manufacturing, and Controls

We limited our analysis of CMC and labeling deficiencies to products that were not approved despite satisfactory safety and efficacy (n = 23). Chemistry, manufacturing, and controls deficiencies included problems with dissolution or manufacturing specifications, incomplete stability data, high endotoxin

levels, and deficiencies noted during inspection of manufacturing facilities.

Table 5 shows the frequency of deficiencies in safety, efficacy, or both and those labeling and manufacturing deficiencies significant enough to prevent approval in the absence of safety or efficacy deficiencies. Efficacy deficiencies were assessed for 89 drugs (48 with efficacy deficiencies only and 41 with both safety and efficacy deficiencies), safety deficiencies for 80 drugs (39 with safety deficiencies only and 41 with both safety and efficacy deficiencies), CMC deficiencies for 19, and labeling deficiencies for 6. The frequency of safety deficiencies was similar among never-approved drugs compared with those with delayed approval (43 of 80 never approved [53.8%] vs 37 of 71 eventually approved [52.1%]; difference, 1.7% [95% CI, -14.86% to 18.05%]; P = .87). However, efficacy deficiencies were significantly more frequent among the never-approved drugs than among those with delayed approvals (61 of 80 never approved [76.3%] vs 28 of 71 eventually approved [39.4%]; difference, 36.9% [95% CI, 20.25% to 50.86%]; P < .001). Among the 48 drugs with initial efficacy concerns alone,

only 31.3% were eventually approved compared with 61.5% of the 39 drugs with safety concerns alone.

Discussion

Between 2000 and 2012, 151 of 302 NMEs (50%) failed to obtain approval when first submitted to the FDA. Of these, 71 were approved during subsequent resubmissions, a median of 435 days later, with an overall approval rate of 73.5% by the end of our study. Applications that were eventually approved were often able to address initial safety, manufacturing, and labeling concerns, but efficacy concerns were less likely to be successfully managed.

Failures late in drug development are costly, often involving the commitment of many study participants and personnel. It is advantageous to identify products that fail as early as possible in the development process to avoid these issues. For those drugs that require resubmission before approval is obtained, delays are taxing on the industry and regulators, and patients may have to wait for access to promising, and sometimes lifesaving, new treatments.⁹

By the time drugs enter the latter stages of development, extensive clinical and nonclinical information is already available and sponsors are often confident about the safety and potential efficacy of investigational drugs. Phase 3 trials provide an opportunity to characterize the size and nature of the clinical effect and the spectrum and frequency of adverse responses, allowing development of a detailed informative drug label. Why then do drugs fail at this advanced stage of development?

We found that some drugs inevitably failed because they proved to be ineffective or unsafe and others failed because the data were inadequate to evaluate safety or efficacy.

Failure to determine the most appropriate dose for clinical use was a major reason for nonapproval. Dosing is frequently decided early in drug development, and optimization of doses to maximize efficacy and minimize toxicity is seldom formally explored in phase 3 studies. Adaptive trial designs¹⁰ and other strategies (such as treating phase 3 trial participants with a randomized sequence of different doses¹¹) may help to optimize doses.

Concerns about the efficacy of NMEs were a frequent reason for failure and proved the most difficult to address. On resubmission, drugs with efficacy concerns were less likely to ultimately get approved than those with safety problems, which could potentially be addressed with appropriate labeling and risk management programs. Similar findings have been reported by others,^{12,13} and late-stage efficacy failures have been ascribed to premature optimism of sponsors related to phase 2 data. Only 31.3% of the drugs with efficacy concerns alone went on to eventual approval compared with 61.5% of the drugs with safety concerns alone.

Among applications failing to prove efficacy, the choice of study end points was often inadequate to demonstrate a clinically meaningful benefit to patients¹⁴ (eg, pain relief, survival, or durable cure). Imperfect surrogate end points have been acceptable in some diseases (eg, the 6-minute walk test

in pulmonary arterial hypertension).¹⁵ In others like cystic fibrosis,¹⁶ Alzheimer disease,¹⁷ and cancer,¹⁸ satisfactory end points for long-term outcomes remain elusive and early responses may not translate into durable responses.¹⁹

When multiple end points were used in a clinical trial and discordant results were obtained for each end point, the FDA frequently concluded that drug efficacy was not proven. Inconsistent findings using more than 1 end point for the same disease have plagued the use of surrogate end points and biological measurements that are not validated,²⁰ and we found them to be more frequent for drugs that were never approved than for those with delayed approval. Approval was also denied when the efficacy of new drugs was judged to be poorer than the standard of care, such that the risks outweighed the benefits. Investigators often overestimate the treatment effect when planning randomized clinical trials,^{21,22} and the clinical benefit of new drugs may not be adequate to justify approval, particularly when other treatments are available.

The most frequent safety concerns preventing approval were clinical adverse events that occurred in phase 3 trials, particularly those affecting the cardiovascular system. The high frequency of cardiac adverse events may be due partly to the range of conditions that were included in this category (thrombotic events, arrhythmic events, and other toxicities to the heart). However, cardiovascular toxicity may escape detection until late in drug development because of poor predictive models.²³ Also, in recent years, the high-profile withdrawals by companies of cyclooxygenase 2 (COX-2) inhibitors have sensitized the drug development community to similar cardiac issues in new drug applications²⁴ and there is increasing reluctance to accept certain levels of risk in the absence of a clear, unmet public health need. Even very large development programs may lack the power to identify serious rare adverse events. As part of the lifecycle approach to drug regulation, safety surveillance continues beyond approval as long as the drug is marketed. Although new findings are frequently addressed in labeling updates, it is unusual to encounter major concerns in licensed products. Of all the NMEs approved during the 12 years of our study, only 1 was withdrawn after marketing for a safety concern. Valdecobix was determined to have an unfavorable risk-to-benefit ratio as a result of its serious cardiac and skin adverse events and was withdrawn from the market in 2005.²⁵

High first-cycle approval rates were associated with drugs granted priority review status for the treatment of serious conditions in which significant improvements in safety or effectiveness compared with available therapies were anticipated. Compared with drugs replicating the existing armamentarium, those qualifying for this incentive addressed areas of medical need with benefits that often outweighed the risks.

Limitations of this study include the lack of objective metrics to determine why drugs fail to obtain marketing approval. In the absence of standard methods, we adopted a heuristic approach to categorizing the reasons for nonapproval. In many cases approval decisions are straightforward. In contentious cases, the FDA has generally relied on public advi-

sory committee meetings with expert consultants for assistance with the regulatory decision. During these meetings, data from the applications are presented by the sponsor and the FDA reviewers, and potential reasons for drug failure are discussed in depth by committee members.⁶ Inevitably, the subtleties of these complex regulatory decisions cannot be fully captured in an aggregated analysis.

Conclusions

We believe that the consensus judgment of experienced FDA reviewers on the reasons for drug failure has provided informative descriptive data. The opportunity to combine the data

from a large number of submissions allowed us to identify categories of drug failure and their relative frequency despite uncertainty associated with certain individual applications. Our findings may be helpful to clinicians and policy makers in interpreting the extensive literature reporting the design and outcome of clinical trials, which in turn may have an effect on practice. For drug developers and clinical investigators, our findings suggest areas of deficiencies in new drug applications in which strategies for drug development could be improved. Early and frequent dialogue between the FDA and drug sponsors addressing critical aspects of study design (including the selection of study populations, study end points, and drug doses) has the potential to reduce delays in the approval of new drugs.²⁶

ARTICLE INFORMATION

Author Contributions: Dr Sacks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sacks, Yasinskaya, Lanthier, Sherman.

Acquisition of data: Sacks, Shamsuddin, Yasinskaya, Lanthier.

Analysis and interpretation of data: Sacks, Shamsuddin, Bouri, Lanthier.

Drafting of the manuscript: Sacks, Shamsuddin, Yasinskaya, Sherman.

Critical revision of the manuscript for important intellectual content: Sacks, Shamsuddin, Bouri, Lanthier.

Statistical analysis: Sacks.

Administrative, technical, or material support: Shamsuddin, Bouri, Lanthier.

Study supervision: Sacks, Sherman.

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