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Health Policy Analysis

Sales Revenues for New Therapeutic Agents Approved by the United States Food and Drug Administration From 1995 to 2014

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ABSTRACT

Objectives: This study aimed to analyze worldwide sales of new therapeutic agents and to estimate the time it takes for product sales to exceed industry-wide average drug development costs.

Methods: Data obtained from company reports were analyzed to track worldwide sales of new medicines approved by the US Food and Drug Administration from 1995 to 2014. All sales figures were reported in 2019 US dollars. Kaplan-Meier curves were used to evaluate the time it took for discounted product sales to exceed the average costs associated with developing 1 new drug (accounting for the costs of failed trials), using published estimates of these costs.

Results: Based on data for 361 of 558 new therapeutic agents approved over the study period (median follow-up 13.2 years), mean sales revenue per product was $15.2 billion through the end of 2019; the median was $6.7 billion. These products jointly generated global sales of $5.5 trillion since approval. Revenues were highly skewed, with the 25 best selling products (7%, 25 of 361) accounting for 38% of this amount ($2.1 trillion of $5.5 trillion). Approximately 47% of products had discounted sales that exceeded the estimated industry-wide average costs of development within 5 years of approval, and 75% within 10 years. After attributing potential production, marketing, and other costs, these numbers dropped to 21% of products within 5 years of approval, and 46% within 10 years.

Conclusions: Sales of new medicines approved from 1995 to 2014 were highly skewed, but many products had net discounted sales that exceeded the industry-wide average costs of development within 10 years of approval. An understanding of how sales revenues accrue in the years after initial approval, alongside data on business costs, can inform discussions about how to incentivize private investment in innovation while ensuring affordable prices for patients and the healthcare system.

Keywords: drug prices, pharmaceutical policy, research and development, revenues.

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Highlights:

- Little is known about how much drug companies earn in sales revenues for new medicines and how long it takes them to recover the costs of research and development.
- Based on data for 361 of 558 new therapeutic agents approved by the US Food and Drug Administration from 1995 to 2014, median worldwide sales per product was $6.7 billion through 2019 (median follow-up 13.2 years). Approximately 2 in 10 drugs had net discounted sales that exceeded the industry-wide average cost of development within 5 years of approval, and 1 in 2 within 10 years of approval (after accounting for production, marketing, and other costs).
- Companies generated large revenues on sales of new drugs approved from 1995 to 2014, although sales were highly skewed. An understanding of the revenues earned by pharmaceutical companies on brand-name drugs, alongside data on business costs, can inform discussions about how to incentivize private investment in innovation while ensuring affordable prices for patients and the healthcare system.

Introduction

New medicines are covered by patents and other forms of market protection, enabling drug companies to charge high prices. Recent studies have placed the median duration of exclusivity for new therapeutic agents in the United States at 12 to 17 years from the time of approval,[1-6] a duration that may be slightly shorter for drugs with larger sales and longer for drugs treating rare diseases and biologics.[4-6] These periods of monopoly protection provide opportunities for manufacturers to earn back investments into the development of new drugs and to make profits.

Previous studies have evaluated global sales revenues in the drug industry. These analyses focused on products approved decades ago (1970s[7] and 1980s[8,9]), had small sample sizes,[7-16] relied partly on sales forecasts (rather than only on historical data),[7-12,17] or looked at sales of specific categories of drugs (cancer therapies,[13,14,18] antibiotics,[15] and monoclonal antibodies[16]). No study has investigated historical sales data for a large sample of recent drug approvals, spanning many drug categories.

This study reports the revenues earned by drug companies from the worldwide sales of 361 new medicines approved by the US Food and Drug Administration (FDA) from 1995 to 2014. It also analyzes how long it took for product sales to exceed industry-wide average drug development costs.

Methods

Sample Identification

Using the Drugs@FDA database, we identified all new medicines—type 1 new drug applications (new molecular entities) and biologics license applications—approved by the US FDA from 1995 to 2014.[19] Restricting the analysis to this timeframe enabled us to gather at least 5 years of data on postapproval sales for each product. We excluded contrast and diagnostic agents, as well as products withdrawn from the US market for safety reasons.

For each agent, we extracted information on the date of approval, indication, type (pharmacologic or biologic), therapeutic area, level of innovation (first in class or next in class), whether the product qualified for any expedited development or approval pathway (accelerated approval, breakthrough, fast track, or priority review), orphan status, route of administration (oral, injection, intravenous, or other), and manufacturer (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015). All data were obtained from the Drugs@FDA database, except information on level of innovation (gathered from publications by FDA officials[20,21]) and therapeutic area (gathered from the anatomical therapeutic chemical classification system database[22]). For agents not yet assigned to a therapeutic area, we categorized the product based on the approved indication.

Data Collection

For each agent, we searched investor reports for information on net worldwide sales of individual products. Although drug companies generally do not disclose net postrebate prices, they frequently report net sales figures, which reflect any confidential rebates or discounts offered by drug companies to payers. An example of the net sales data reported by 1 company is presented in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015.

For publicly traded US companies, we searched the Securities and Exchange Commission website for annual 10-K forms, which contain audited financial statements with data on net product sales.[23] For foreign and private US companies, we searched the company websites for annual reports to investors for information on net product sales.

We extracted product sales from the date of approval to December 31, 2019; for some Japanese firms, we pulled data through March 31, 2020, given that most Japanese companies operate on a fiscal year that ends in March. We used the date of approval by the US FDA as the starting point given that most new pharmaceutical products are first approved in the United States.[21]

Some companies partnered with other firms to commercialize their products in certain markets, sometimes using different brand names. For those products, we gathered data on net sales from all partners. If the company that developed the product reported sales on behalf of all commercial partners, we did not include sales from partners to avoid double counting. If a company sold or licensed the marketing rights of a product to another firm, then we continued tracking net sales for the firm that acquired the marketing rights. We excluded revenues from milestone or royalty payments given that our analysis focused on net product sales.

We only included products for which we had sales data for at least 70% of the years since approval (or 70% of the years from approval up until loss of exclusivity if the company stopped reporting at that point). For included agents, we used linear interpolation to impute missing data, as was done in a previous study.[13] In total, 7% of annual sales figures in our sample (351 of 5109) were imputed, corresponding to 1% of total revenue ($63.1 billion / $5.5 trillion).

Two investigators (OJW and JL) independently collected sales data to ensure accuracy. Foreign currencies were converted to US dollars using yearly average foreign exchange rates. To account for inflation, all sales figures were adjusted to 2019 US dollars using the US gross domestic product deflator.

Statistical Analysis

χ^2 tests were used to identify statistically significant differences in the characteristics of the products in our sample compared with those of all novel agents approved by the FDA from 1995 to 2014.

We calculated the mean and median total global sales in our sample, with 95% CIs (bootstrapped for medians), with results broken down by lifetimes sales (since FDA approval) versus sales in the first 5 and 10 years on the market (to standardize revenues given that products may have been on the market for varying amounts of time). We also reported mean and median amounts by therapeutic area and other drug categories. Kruskal-Wallis and Mann-Whitney U tests were used to identify differences in median sales between therapeutic areas and other drug categories.

Kaplan-Meier curves were used to estimate the proportion of therapeutics that had sales that exceeded estimates of average industry-wide development costs. We used published estimates of the mean development costs to determine when a product might have "broken even," as done in previous analyses.[7,8,10,12,13,17] DiMasi et al[24] estimated the mean expenditure at $1.2 billion (2019 US dollars) for products developed in the 1990s to mid-2000s, whereas a more recent study by Wouters et al[25] estimated this amount to have increased to $1.6 billion (2019 US dollars) for products developed in the 2000s to 2010s; both estimates accounted for the costs of failed trials and the cost of capital (ie, required rate of return for investors). We used the earlier estimate ($1.2 billion) as the presumed break-even point for products in our sample approved from 1995 to 2004 (first half of the period), and the more recent estimate ($1.6 billion) for products approved from 2005 to 2014 (second half). We discounted the revenues at 10.5% (the same rate used to capitalize development expenses[25,26]) to calculate net present values.

We ran 3 additional analyses. First, given that our estimates of the time it took companies to recover costs were sensitive to the assumed development costs, we recalculated the results using a threshold of $2.8 billion for products approved from 2005 to 2014, based on a recent alternative estimate by DiMasi et al.[26] Second, we re-estimated how long it took companies to recover development costs after deducting 60% from the annual sales figures for each product to account for expenses incurred for selling, general, and administrative activities (which includes marketing and distribution), production (usually referred to in investor reports as the costs of goods sold), and depreciation and amortization (which reflects the decrease in value of physical assets, such as factory equipment, over their useful lifespans). The deduction was based on an estimate of the average cost breakdown in the pharmaceutical industry in 2014: as a percentage of net sales, the costs of selling, general, and administrative activities were pegged at 27%, production 25%, and depreciation and amortization 8%.[27] These percentages are in line with estimates from other sources.[28-30] Third, because the products that were excluded from our sample due to missing data likely included a disproportionate number of low-selling drugs, we performed a rerun of the Kaplan-Meier analysis after imputing sales figures for these products

corresponding to the revenue earned by the drug at the 25th percentile in our sample, and then another rerun using the revenue earned by the drug at the 10th percentile.

All statistical tests were 2 sided, with $P < .05$ considered significant. The data were analyzed in R, version 4.2 (R Foundation for Statistical Computing). The study was exempt from institutional review board approval given that all data were publicly available. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[31]

Results

The US FDA approved 616 new drugs and biologics from 1995 to 2014; 58 were excluded for being contrast agents or withdrawn for safety reasons. Sales data were available for 361 products (65%, 361 of 558), sold by 126 different companies (Fig. 1). The follow-up time in our sample ranged from 5 years to 25 years, with a median of 13.2 years of sales data per product (Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

Sample Characteristics

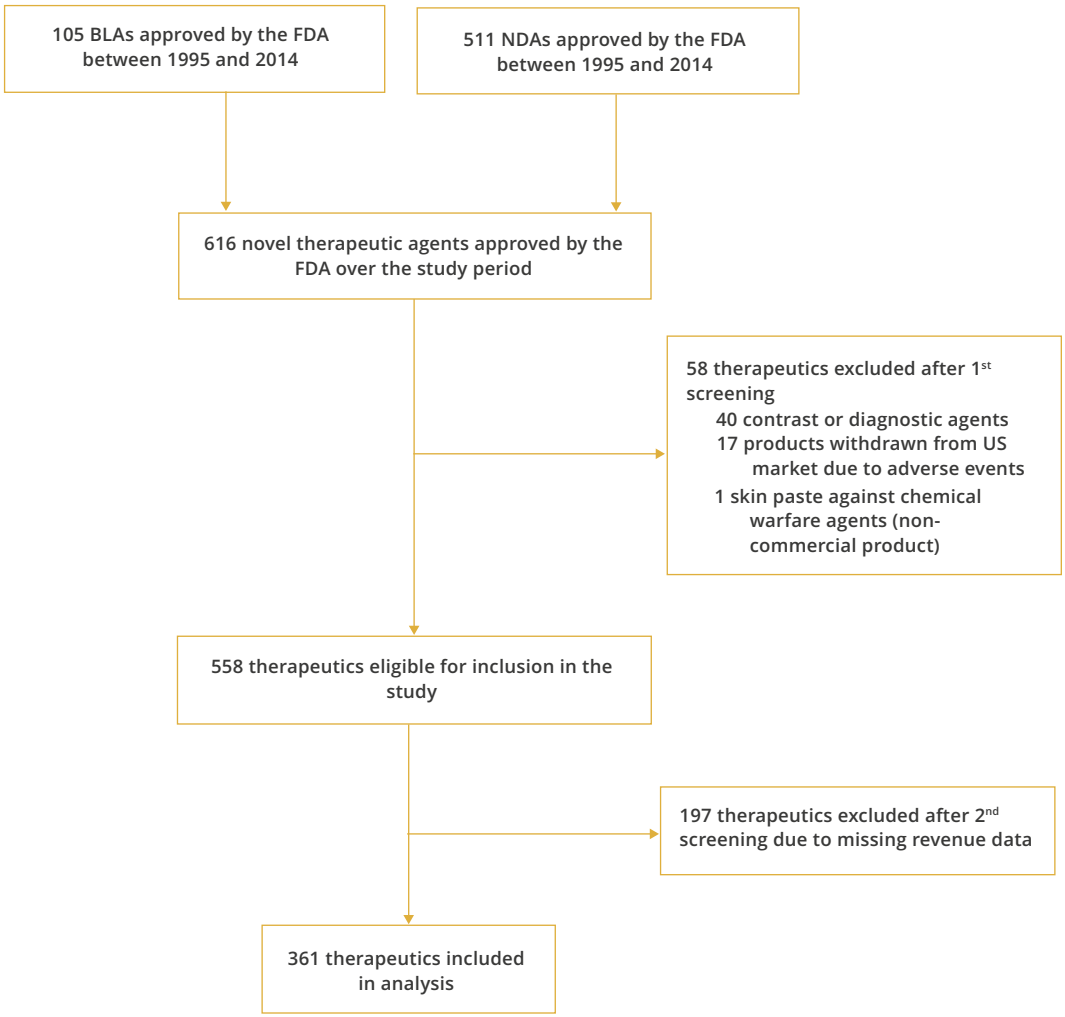
The sample had a larger share of biologic agents and nonrare-disease drugs than all novel therapeutics approved by the FDA over the study period (Table 1), but these differences were not statistically significant. Differences in the distribution by therapeutic category, route of administration, and approval years were statistically significant.

Sales Data

The 361 products generated global sales of $5.5 trillion during the study period, an average of $15.2 billion per product (95% CI $12.8 billion to $17.7 billion). The median sales revenue in our sample was $6.7 billion (interquartile range [IQR] $2.5 billion to $18.5 billion) (Table 2). Revenues were highly skewed, with the 25 best selling products (7%, 25 of 361) accounting for 38% of total revenues in our sample over the study period ($2.1 trillion of $5.5 trillion) and the 50 best selling products (14%, 50 of 361) accounting for 56% of the total ($3.1 trillion of $5.5 trillion).

The mean revenue per product was $3.2 billion after 5 years (n = 361), $9.5 billion after 10 years (for the n = 254 products that

Figure 1. Flowchart of sample selection.



BLA indicates a biologics license application; FDA, Food and Drug Administration; NDA, new drug application.

Table 1. Characteristics of novel therapeutics approved by the US FDA from 1995 to 2014.

Characteristics	N (%)*		*P* value
	Included agents (n = 361)	All approvals (n = 558)	
Agent type			
Pharmacologic	295 (82)	464 (83)	.27
Biologic	66 (18)	94 (17)	
Therapeutic area			
Antineoplastic and immunomodulating agents	103 (29)	137 (25)	<.001
Nervous system	51 (14)	73 (13)	
Alimentary tract and metabolism	48 (13)	67 (12)	
Anti-infectives for systemic use	45 (12)	68 (12)	
Cardiovascular system	25 (7)	38 (7)	
Blood and blood forming organs	18 (5)	28 (5)	
Genitourinary system and sex hormones	15 (4)	25 (4)	
Respiratory system	15 (4)	23 (4)	
Sensory organs	12 (3)	23 (4)	
Musculoskeletal system	12 (3)	15 (3)	
Various	9 (2)	24 (4)	
Dermatologicals	4 (1)	20 (4)	
Systemic hormonal preparations, excluding sex hormones and insulins	4 (1)	11 (2)	
Antiparasitic products, insecticides, and repellents	0 (0)	6 (1)	
Orphan drug	93 (26)	155 (28)	.18
Drug received accelerated approval	46 (13)	67 (12)	.56
Drug qualified for an expedited development or approval pathway[†]	192 (53)	295 (53)	.91
First in class			
Yes	126 (35)	194 (35)	>.99
No	235 (65)	364 (65)	
Route of administration[‡]			
Oral	213 (59)	295 (53)	<.001
Injection	75 (21)	120 (22)	
Intravenous	28 (8)	47 (8)	
Other	45 (12)	96 (17)	
Year of approval			
1995-2004	177 (49)	308 (55)	<.001
2005-2014	184 (51)	250 (45)	

FDA indicates Food and Drug Administration.
*Percentages do not always add to 100% due to rounding. χ^2 tests were conducted on the data for included agents (n = 361) vs excluded ones (n = 197).
[†]Included accelerated approval, breakthrough therapy, fast track, orphan drug, and priority review.
[‡]Oral included capsules, suspensions, solutions, and tablets. Injection included intramuscular, intraperitoneal, intrathecal, intravitreal, and subcutaneous. Other routes included inhalation, ophthalmic, otic, topical, and vaginal, as well as products with multiple routes of administration.

were observed up to 10 years), and $19.2 billion after 15 years (n = 177). Because of the skewed nature of the data, the median revenue per product was lower at $1.7 billion after 5 years (and with IQR of $0.7-3.8 billion), $5.3 billion after 10 years (IQR $2.4-11.2 billion), and $10.2 billion after 15 years (IQR $5.0-23.1 billion).

Sales since approval were less than $1 billion for 48 drugs (13%, 48 of 361), $1 billion to less than $5 billion for 101 drugs (28%), $5 billion to less than $10 billion for 77 drugs (21%), $10 billion to less than $50 billion for 111 drugs (31%), $50 billion to less than $100 billion for 18 products (5%), and more than $100 billion for 6 products (2%) (Fig. 2).

A total of 178 drugs (49%, 178 of 361) had sales of ≥$1 billion in their peak year, the usual threshold for a product to be considered a "blockbuster" seller; 109 products (30%, 109 of 361) averaged ≥$1 billion in sales per year since approval. Worldwide sales (since approval) of each product in our sample are presented in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015.

Sales by Therapeutic Area and Other Drug Categories

Median 5-year sales by therapeutic area (for areas with ≥10 drugs) ranged from $1.1 billion (95% CI $0.1 billion to $1.6 billion) for sensory organ agents to $3.0 billion (95% CI $0.9 billion to $3.6 billion) for genitourinary agents and sex hormones (Table 2). Differences in medians between therapeutic areas were statistically significant (at $P = .04$).

Median 5-year sales for rare-disease drugs were lower ($1.0 billion; 95% CI $0.7 billion to $1.6 billion) than for nonrare-disease drugs ($1.9 billion; 95% CI $1.6 billion to $2.3 billion) ($P < .001$). Median 5-year sales for drugs that received accelerated approval were $1.9 billion (95% CI $1.5 billion to $2.9 billion) compared with $1.6 billion (95% CI $1.5 billion to $1.9 billion) for drugs that did

Table 2. Revenues from worldwide sales of novel therapeutics approved by the US FDA from 1995 to 2014 (by drug category).

Characteristics	Global sales in $, billions (95% CI)					
	First 5 years since approval		*P* value[†]	First 10 years since approval		*P* value[†]
	Median	Mean*		Median	Mean*	
Full sample (n = 254 for 10-year results and n = 361 for 5-year results)	1.7 (1.5-1.9)	3.2 (2.7-3.6)	-	5.3 (4.4-6.1)	9.5 (8.0-10.9)	-
Agent type						
Pharmacologic (n = 214 and n = 295)	1.6 (1.4-1.9)	3.0 (2.5-3.4)	.14	4.9 (4.0-5.9)	8.7 (7.1-10.2)	.03
Biologic (n = 40 and n = 66)	2.3 (1.5-3.4)	4.2 (2.9-5.5)		9.8 (5.2-14.2)	13.7 (9.3-18.0)	
Therapeutic area						
Antineoplastic and immunomodulating agents (n = 63 and n = 103)	2.2 (1.7-3.0)	3.7 (2.8-4.5)	.04	7.8 (5.3-11.0)	11.5 (8.6-14.4)	.01
Nervous system (n = 41 and n = 51)	1.5 (0.8-2.2)	2.7 (1.7-3.7)		5.2 (3.1-6.9)	8.7 (5.0-12.3)	
Alimentary tract and metabolism (n = 31 and n = 48)	1.7 (0.8-2.8)	2.9 (2.0-3.8)		5.3 (2.9-8.3)	9.1 (5.6-12.6)	
Anti-infectives for systemic use (n = 32 and n = 45)	1.6 (1.1-2.2)	3.2 (1.4-4.9)		4.9 (2.7-6.6)	5.4 (4.0-6.9)	
Cardiovascular system (n = 20 and n = 25)	1.7 (1.1-2.5)	3.6 (1.2-6.1)		7.4 (4.2-19.0)	16.0 (5.1-27.0)	
Blood and blood forming organs (n = 13 and n = 18)	1.5 (0.6-5.0)	3.9 (1.4-6.4)		3.3 (2.5-4.9)	8.6 (0.4-16.8)	
Genitourinary system and sex hormones (n = 13 and n = 15)	3.0 (0.9-3.6)	2.8 (1.4-4.3)		9.6 (2.3-11.4)	8.9 (4.9-12.8)	
Respiratory system (n = 9 and n = 15)	2.5 (1.0-3.7)	3.3 (1.6-4.9)		8.7 (2.7-27.9)	13.5 (4.5-22.4)	
Sensory organs (n = 9 and n = 12)	1.1 (0.1-1.6)	3.3 (0-6.7)		3.0 (1.3-10.0)	6.8 (0-14.9)	
Musculoskeletal system (n = 9 and n = 12)	2.2 (0.9-5.0)	3.8 (0.6-7.0)		7.8 (3.6-14.6)	11.1 (2.8-19.3)	
Various (n = 7 and n = 9)	0.6 (0.1-1.6)	0.9 (0.2-1.6)		2.3 (0.6-4.3)	2.7 (0.3-5.1)	
Dermatologicals (n = 3 and n = 4)	0.5 (0-1.5)	0.6 (0-1.76)		0.8 (0.01-2.4)	1.1 (0-4.1)	
Systemic hormonal preparations, excluding sex hormones and insulins (n = 4 and n = 4)	0.8 (0.08-2.1)	0.9 (0-2.5)		2.3 (0.3-7.8)	3.2 (0-8.7)	
Orphan drug						
Yes (n = 54 and n = 93)	1.0 (0.7-1.6)	2.3 (1.5-3.1)	< .001	3.2 (1.8-5.0)	6.3 (4.1-8.5)	.002
No (n = 200 and n = 268)	1.9 (1.6-2.3)	3.5 (3.0-4.0)		5.9 (4.9-7.4)	10.3 (8.6-12.0)	
Drug received accelerated approval						
Yes (n = 33 and n = 46)	1.9 (1.5-2.9)	3.8 (2.2-5.4)	.30	6.4 (5.2-11.3)	9.2 (6.2-12.3)	.36
No (n = 221 and n = 315)	1.6 (1.5-1.9)	3.1 (2.6-3.6)		4.9 (4.0-6.1)	9.5 (7.9-11.1)	
Drug qualified for an expedited development or approval pathway[‡]						
Yes (n = 130 and n = 192)	1.7 (1.5-2.1)	3.5 (2.7-4.2)	.71	5.0 (3.9-6.4)	9.2 (7.4-11.1)	.77
No (n = 124 and n = 169)	1.6 (1.4-2.0)	2.9 (2.4-3.4)		5.4 (4.3-7.4)	9.7 (7.4-11.9)	
First in class						
Yes (n = 77 and n = 126)	1.6 (1.1-2.0)	3.4 (2.5-4.3)	.75	4.8 (3.1-7.1)	9.0 (6.5-11.5)	.46
No (n = 177 and n = 235)	1.7 (1.5-2.1)	3.1 (2.6-3.6)		5.7 (4.4-6.5)	9.6 (7.8-11.5)	
Route of administration[§]						
Oral (n = 152 and n = 213)	2.0 (1.6-2.4)	3.5 (2.9-4.1)	.02	6.1 (5.3-7.4)	10.1 (8.1-12.1)	.04
Injection (n = 49 and n = 75)	1.5 (1.0-2.2)	3.0 (2.0-4.1)		4.4 (3.0-8.7)	8.8 (5.7-11.9)	
Intravenous (n = 15 and n = 28)	1.6 (0.4-2.9)	3.2 (1.3-5.1)		5.6 (2.8-19.2)	13.1 (5.0-21.3)	
Other (n = 38 and n = 45)	1.1 (0.8-1.6)	2.0 (1.1 –2.9)		2.8 (2.2-4.5)	6.2 (3.5-8.9)	

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Table 2. Continued

Characteristics	Global sales in $, billions (95% CI)					
	First 5 years since approval		*P* value†	First 10 years since approval		*P* value†
	Median	Mean*		Median	Mean*	
Year of approval						
1995-2004 (n = 177 and n = 177)	1.9 (1.5-2.4)	3.3 (2.7-3.8)	.19	6.1 (5.1-7.8)	10.9 (8.9-12.8)	.001
2005-2014 (n = 77 and n = 184)	1.6 (1.3-1.8)	3.1 (2.4-3.8)		3.7 (2.6-5.2)	6.2 (4.5-7.8)	

FDA indicates Food and Drug Administration.
*Negative lower limits for the 95% CIs were replaced with zeros.
†Kruskal-Wallis and Mann-Whitney U tests were conducted to compare differences in the median revenue figures. *P* values were not adjusted for multiple comparisons.
‡Included accelerated approval, breakthrough therapy, fast track, orphan drug, and priority review.
§Oral included capsules, suspensions, solutions, and tablets. Injection included intramuscular, intraperitoneal, intrathecal, intravitreal, and subcutaneous. Other routes included inhalation, ophthalmic, otic, topical, and vaginal, as well as products with multiple routes of administration.

not receive accelerated approval. This difference was not statistically significant (*P* = .30). Median 5-year sales for first-in-class therapies were $1.6 billion (95% CI $1.1 billion to $2.0 billion) compared with $1.7 billion (95% CI $1.5 billion to $2.1 billion) for products that were not first in class. This difference was also not significant (*P* = .75) (Table 2).

For most categories, the statistical significance of differences in median revenues between drug categories did not change when looking at 10-year sales since approval (instead of 5-year sales), apart from the results for year of approval and agent type. Drugs approved from 1995 to 2004 recorded higher 10-year revenues than drugs approved from 2005 to 2014 (*P* = .001). Biologics recorded higher 10-year revenues than pharmacologic agents (*P* = .03)

Time to Recovery of Estimated Industry-Wide Average Development Costs

Without discounting, the unadjusted Kaplan-Meier curve showed that 57.1% of products (95% CI 51.6%-61.9%) had sales that exceeded the estimated industry-wide average costs of development within 5 years of approval, 83.1% (95% CI 78.3%-86.9%) within 10 years, and 87.1% (95% CI 82.1%-90.7%) within 15 years (these results are not shown in any figure or table).

With revenues discounted at 10.5% (ie, the base-case analysis), the unadjusted Kaplan-Meier curve showed that 47.1% of products (95% CI 41.7%-52.0%) had sales that exceeded the estimated industry-wide average costs of development within 5 years of approval, 75.2% (95% CI 69.9%-79.6%) within 10 years, and 81.8% (95% CI 76.2%-86.1%) within 15 years (Fig. 3).

After accounting for production costs (25% reduction to annual sales) and discounting revenues at 10.5%, the unadjusted Kaplan-Meier curve showed that 38.8% of products (95% CI 33.5%-43.6%) recovered estimated industry-wide average costs within 5 years of approval, 68.2% (95% CI 62.5%-73.0%) within 10 years, and 77.4% (95% CI 71.4%-82.2%) within 15 years (Fig. 3).

After accounting for production, marketing, and other costs (60% reduction to annual sales) and discounting at 10.5%, the unadjusted Kaplan-Meier curve showed that 20.5% of products (95% CI 16.2%-24.9%) recovered estimated industry-wide average costs within 5 years of approval, 45.6% (95% CI 39.9%-50.8%) within 10 years, and 56.2% (95% CI 49.7%-61.9%) within 15 years (Fig. 3).

When both discounting revenues at 10.5% and applying the higher figure for development costs (ie, $2.8 billion) as the cost-recovery threshold for products approved from 2005 to 2014, the unadjusted Kaplan-Meier curve showed that 39.6% of products (95% CI 34.4%-44.5%) recovered estimated industry-wide average costs within 5 years of approval, 65.4% (95% CI 59.6%-70.4%) within 10 years, and 73.6% (95% CI 67.3%-78.7%) within 15 years (Appendix Fig 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

When discounting revenues at 10.5%, applying the higher figure for development costs, and accounting for production, marketing, and other costs, the unadjusted Kaplan-Meier curve showed that 16.3% of products (95% CI 12.4%-20.1%) recovered estimated industry-wide average costs within 5 years of approval, 37.6% (95% CI 32.0%-42.7%) within 10 years, and 51.0% (95% CI 44.3%-56.8%) within 15 years (Appendix Fig 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

No sales data were available for 197 of the 558 products approved over the study period (35%, 197 of 558). When we reran the base-case analysis with imputations done for these products based on sales revenues at the 25th percentile ($2396.1 million, assumed to be evenly spread out since approval), the unadjusted Kaplan-Meier curve showed that 32.4% of products (95% CI 28.4%-36.2%) recovered average estimated costs within 5 years of approval, 54.9% (95% CI 50.4%-58.9%) within 10 years, and 63.0% (95% CI 58.5%-67.1%) within 15 years (Appendix Fig 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

Rerunning the base-case analysis with imputations done at the 10th percentile ($753.3 million), the unadjusted Kaplan-Meier curve showed that 30.5% of products (95% CI 26.5%-34.2%) recovered estimated industry-wide average costs within 5 years of approval, 48.0% (95% CI 43.5%-52.2%) within 10 years, and 51.2% (95% CI 46.3%-55.1%) within 15 years (Appendix Fig 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

We also reran the base-case analysis under the following conditions: (1) imputations done for missing products based on the sales revenues at the 10th percentile ($753.3 million), (2) cost-recovery threshold based on the higher estimate of development costs ($2.8 billion) for products approved from 2005 to 2014, and (3) adjustments for production, marketing, and other costs (60% reduction to annual sales). In this scenario, the unadjusted Kaplan-Meier curve showed that 10.5% of products (95% CI 8.0%-13.1%) recovered estimated industry-wide average costs within 5 years of approval, 23.9% (95% CI 20.1%-27.5%) within 10 years, and 31.2% (95% CI 26.7%-35.3%) within 15 years (Appendix Fig 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.015).

Discussion

Based on data for 361 of 558 new therapeutic agents approved by the US FDA from 1995 to 2014, median sales per product was $6.7 billion through the end of 2019 (median

Figure 2. Sales since approval for each product in the sample (with products grouped by year of approval).

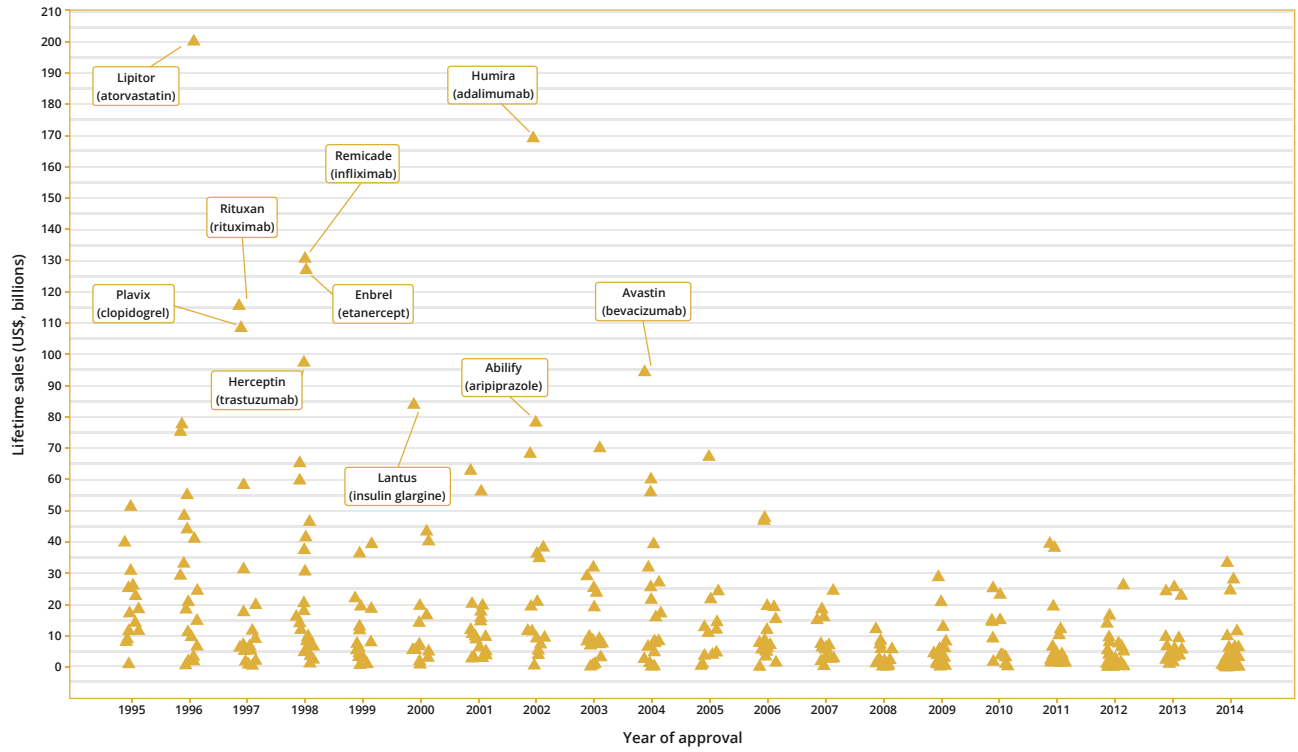
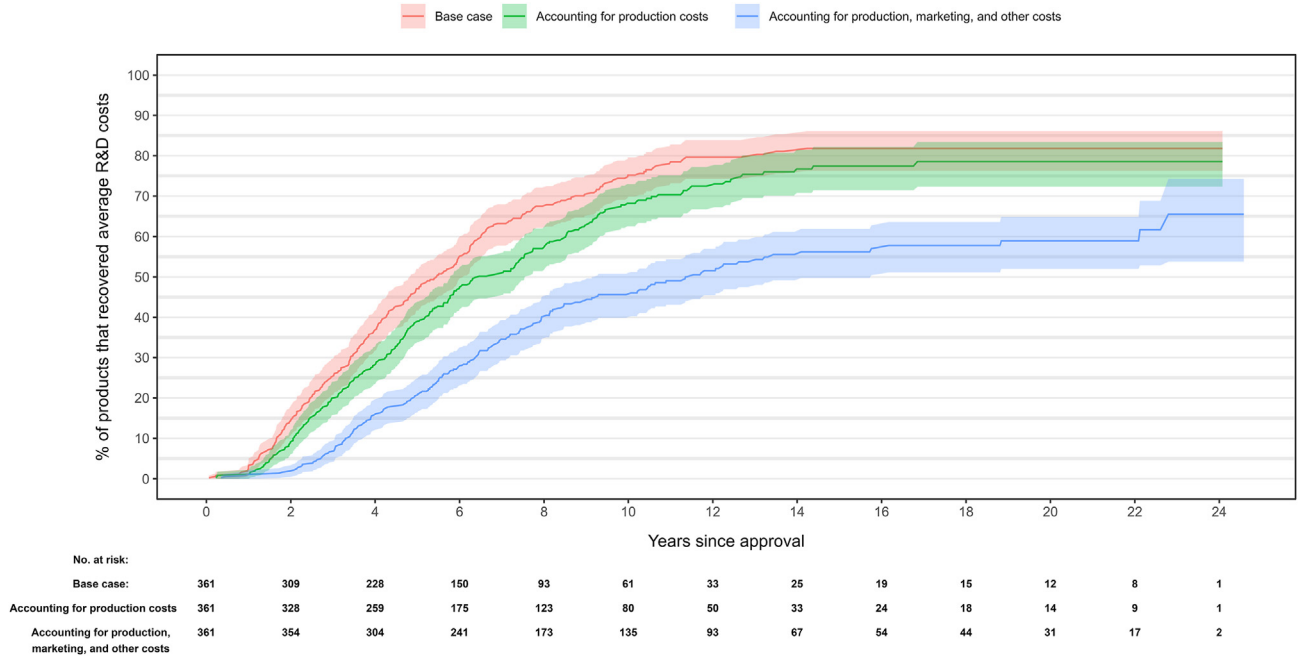


Figure 3. Proportion of therapeutics that recovered costs over time (shaded areas represent 95% CIs). This figure shows the complements of the Kaplan-Meier survival functions. One or 2 products (depending on the curve) were censored past the 24-year mark, hence why the risk sets show 1 to 2 products remaining at that point. The estimate of drug development costs from DiMasi et al[24] ($1.2 billion) was used as the cost-recovery threshold for products approved from 1995 to 2004, and the estimate from Wouters et al[25] ($1.6 billion) was used for products approved from 2005 to 2014. We discounted the revenues at 10.5% (the same rate used to capitalize development expenses[24,25]) to calculate net present values.



R&D indicates research and development.

follow-up 13.2 years). Revenues were highly skewed, with the 50 best selling products accounting for 56% of the $5.5 trillion that these 361 products generated in global sales since approval. Antineoplastic, immunomodulating, and cardiovascular drugs were among those that brought in the most sales for drug companies. Sales for rare-disease drugs were lower than for drugs to treat more common conditions. In the base-case analysis, the Kaplan-Meier analysis showed that approximately half of products (47%) had sales that exceeded the industry-wide estimated development costs within 5 years of FDA approval, and a majority (75%) within 10 years. After accounting for production, marketing, and other costs, 46% products were estimated to have recovered costs within 10 years.

High-grossing drugs can compensate for many failures, which are far more likely to occur early in the development process when the least amount is invested. For instance, atorvastatin on its own made $200.1 billion in sales since approval. The distribution of sales data was overall highly skewed, with a total of 135 products in our sample generating sales of $10 billion or more since approval. Some large pharmaceutical companies hold several of these products in their portfolios. At the other end of the sales distribution, our results suggest that approximately 1 in 8 drugs (13%) generated less than $1 billion in sales even after at least 5 years on the market.

Our observations are in line with the results of 2 recent studies finding that cumulative sales revenues for cancer drugs generally eclipsed the costs of development.[13,14] Tay-Teo et al[13] tracked sales of 99 cancer drugs from 1989 to 2017 and estimated that every dollar spent on the development for these drugs generated a median of $14.50 in sales. They estimated that the median time for drug companies to recoup the costs of development was 5 years,[13] although they did not account for censoring (due to lack of data for recently approved drugs). Prasad and Mailankody[14] reported global sales of 10 cancer drugs in 2006 to 2015 and found that these products generated $67 billion in sales versus the estimated $7.2 billion spent to develop them.

Berndt et al[17] reported a decline in sales revenues for drugs approved in 2005 to 2009 compared with drugs approved in 1995 to 2004. The authors of that study estimated that the average drug approved in 2005 to 2009 failed to recoup development, production, marketing, and other costs over their lifetime, based on estimates of average expenses related to these activities in the drug industry. We similarly observed that, after accounting for production, marketing, and other costs, 46% of medicines recouped average costs of development within 10 years of approval. However, these estimates were highly dependent on assumptions about the magnitude of business expenses. Further validation work is needed to establish the exact amounts spent on these activities.

The Inflation Reduction Act of 2022 directs the Centers for Medicare & Medicaid Services to negotiate the prices of top-selling medicines that have been on the market for at least 9 to 13 years. As part of this negotiation process, the government agency will examine the net prices of therapeutic alternatives to the drugs selected for negotiation, as well as their relative clinical benefits and risks, to arrive at initial price offers. Medicare will also consider other factors as part of the negotiation process, such as whether manufacturers have recouped the costs of development by the time their products are subject to negotiation; the agency may adjust the negotiated price higher if a firm has not recouped these costs. An understanding of the revenues earned by pharmaceutical companies on brand-name drugs, alongside data on business costs, can inform discussions about how to incentivize private investment in innovation while ensuring affordable prices for patients and the healthcare system.

Limitations

First, sales data were missing for 35% of new medicines (197 of 558) approved by the FDA from 1995 to 2014. Some drug companies may have selectively reported high-selling products, which would limit the generalizability of the results to all new therapeutic agents. The agents included in our sample differed from other medicines approved by the FDA during the study period, although most differences were not statistically significant.

Second, we are likely to have underestimated sales since approval for some products because data were not always available for all marketing partners worldwide. In addition, we did not capture revenues from sales before the date of FDA approval (for products first launched outside the United States).

Third, our use of industry-wide estimates of average expenses related to development, production, marketing, and other business activities may have led us to over- or underestimate the performance of individual products. This approach allowed us to generate industry-wide estimates of the profitability of new products, as done in previous analyses.[7,8,10,12,13,17] Although cost data for individual products would allow for the estimation of profits at a more granular level, such analyses will only be possible if companies are more transparent about drug development costs and make these data available.

Fourth, the estimates of industry-wide average research and development costs used in our study were sourced from earlier analyses, which had limitations. Those studies relied on aggregate clinical trial success rates to account for the costs of failed trials, which may have over- or underestimated actual costs for individual products; estimates of development costs were also heavily dependent on assumptions around the cost of capital (ie, required rate return for investors). Average development costs may vary by product category (eg, orphan vs nonorphan drugs, biologics vs small-molecule drugs).

Conclusions

Drug companies generated substantial revenues on the sales of new medicines approved by the US FDA from 1995 to 2014, although sales were highly skewed. In the base-case analysis, 75% of products had net discounted sales that exceeded the average costs of development within 10 years of approval, although that percentage was lower in some of the analyses that also accounted for other business costs. Further research using product-specific data on drug development costs, should these be made publicly available by drug companies, would improve upon our estimates.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material section.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2024.06.015.

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REFERENCES

1. Kesselheim AS, Sinha MS, Avorn J. Determinants of market exclusivity for prescription drugs in the United States. *JAMA Intern Med*. 2017;177(11):1658–1664.
2. Wang B, Liu J, Kesselheim AS. Variations in time of market exclusivity among top-selling prescription drugs in the United States. *JAMA Intern Med*. 2015;175(4):635–637.
3. Raimond VC, Feldman WB, Rome BN, Kesselheim AS. Why France spends less than the United States on drugs: a comparative study of drug pricing and pricing regulation. *Milbank Q*. 2021;99(1):240–272.
4. Grabowski H, Long G, Mortimer R, Bilginsoy M. Continuing trends in U.S. brand-name and generic drug competition. *J Med Econ*. 2021;24(1):908–917.
5. Grabowski HG, Kyle M. Generic competition and market exclusivity periods in pharmaceuticals. *Manag Decis Econ*. 2007;28(4-5):491–502.
6. Grabowski H, Long G, Mortimer R, Boyo A. Updated trends in US brand-name and generic drug competition. *J Med Econ*. 2016;19(9):836–844.
7. Grabowski H, Vernon J. A new look at the returns and risks to pharmaceutical R&D. *Manag Sci*. 1990;36(7):804–821.
8. Grabowski HG, Vernon JM. Returns to R&D on new drug introductions in the 1980s. *J Health Econ*. 1994;13(4):383–406.
9. Cook A. How increased competition from generic drugs has affected prices and returns in the pharmaceutical industry. http://www.cbo.gov/; Published 1998. Accessed May 24, 2022.
10. Grabowski HG, Vernon J. The distribution of sales revenues from pharmaceutical innovation. *Pharmacoeconomics*. 2000;18(suppl 1):21–32.
11. DiMasi JA, Grabowski HG, Vernon J. R&D costs and returns by therapeutic category. *Drug Inf J*. 2004;38(3):211–223.
12. Grabowski H, Vernon J, DiMasi JA. Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics*. 2002;20(suppl 3):11–29.
13. Tay-Teo K, Ilbawi A, Hill SR. Comparison of sales income and Research and Development costs for FDA-approved cancer drugs sold by originator drug companies. *JAMA Netw Open*. 2019;2(1):e186875.
14. Prasad V, Mailankody S. Research and Development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med*. 2017;177(11):1569.
15. Rahman S, Lindahl O, Morel CM, Hollis A. Market concentration of new antibiotic sales. *J Antibiot*. 2021;74(6):421–423.
16. Walsh G. Biopharmaceutical benchmarks 2018. *Nat Biotechnol*. 2018;36(12):1136–1145.
17. Berndt ER, Nass D, Kleinrock M, Aitken M. Decline in economic returns from new drugs raises questions about sustaining innovations. *Health Aff (Proj Hope)*. 2015;34(2):245–252.
18. Brinkhuis F, Goettsch WG, Mantel-Teeuwisse AK, Bloem LT. Added benefit and revenues of oncology drugs approved by the European Medicines Agency between 1995 and 2020: retrospective cohort study. *BMJ*. 2024;384:e077391.
19. US Food and Drug Administration. Drugs@FDA: FDA approved drug products. https://www.accessdata.fda.gov/scripts/cder/daf/; Published 2021. Accessed April 14, 2021.
20. Lanthier M, Miller KL, Nardinelli C, Woodcock J. An improved approach to measuring drug innovation finds steady rates of first-in-class pharmaceuticals, 1987-2011. *Health Aff*. 2013;32(8):1433–1439.
21. US Food and Drug Administration. Novel Drug Approvals at FDA. https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda; Published 2022. Accessed July 15, 2024.
22. WHO Collaborating Center for Drug Statistics Methodology. ATC/DDD index 2021. https://www.whocc.no/atc_ddd_index/; Published 2021. Accessed April 15, 2021.
23. US Securities and Exchange Commission. EDGAR company filings. https://www.sec.gov/edgar/searchedgar/companysearch.html; Published 2020. Accessed July 10, 2020.
24. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22(2):151–185.
25. Wouters OJ, McKee M, Luyten J. Estimated Research and Development investment needed to bring a new medicine to market, 2009-2018. *JAMA*. 2020;323(9):844–853.
26. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20–33.
27. McKinsey & Company. Rethinking Pharma productivity. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rethinking-pharma-productivity; Published 2017. Accessed April 12, 2021.
28. Boston Consulting Group. Getting a grip on COGS in generic drugs. https://www.bcg.com/en-gb/publications/2019/getting-a-grip-on-cogs-in-generic-drugs; Published 2019. Accessed April 12, 2021.
29. Gagnon MA, Lexchin J. The cost of pushing pills: a new estimate of pharmaceutical promotion expenditures in the United States. *PLOS Med*. 2008;5(1):e1.
30. Basu P, Joglekar G, Rai S, Suresh P, Vernon J. Analysis of manufacturing costs in pharmaceutical companies. *J Pharm Innov*. 2008;3(1):30–40.
31. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet (London, England)*. 2007;370(9596):1453–1457.