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ABSTRACT

Purpose: This work describes the late-stage product portfolios of the biotechnology companies that completed initial public offerings (IPOs) from 1997 to 2016. We asked whether these emerging companies continue to develop innovative, biologic products and produce the innovation promised by the early biotechnology industry.

Methods: We identified therapeutic products that reached Phase III development from 1997 to 2016, the characteristics of the products, the dates of the initiation of Phase III and product approval, proxy indicators of the innovativeness of each product, and the contribution of each biotechnology company. Companies were characterized by IPO window and clinical status of the most advanced product at IPO. Time from IPO to Phase III or approval, and the estimated probability of a company having a product advance to these milestones, were examined using Kaplan–Meier analysis.

Findings: A total of 319 biotechnology companies completed IPOs from 1997 to 2016. These companies contributed to the development of 367 products that progressed to Phase III, and of 144 new drug approvals, through 2016. The estimated probability of a company having a product reach Phase III was 78%, and the estimated probability of a company receiving at least 1 product approval was 52%, with most approvals occurring >5 years after IPO. Small-molecule drugs represented 74% of products reaching Phase III and 78% of approvals. Reformulations represented 36% of Phase III products and 46% of approvals. The estimated probability of product approval was significantly higher for reformulations than new molecular entities (NMEs) and slightly higher for small molecules than biologics. The estimated probability of a company receiving product approval varied significantly by IPO window and was greater for companies with Phase III products at IPO (74%). These companies contributed to the development of 78 NMEs, 44% of which were classified as first in class, initiating development of 69% and contributing to the clinical development of 96%. These products represented 16% of all NMEs and 28% of biologics approved between 1997 and 2016. Seven products achieved per-annum sales of >$1 billion during the study period.

Implications: The majority of emerging publicly owned biotechnology companies contribute to products that advance to Phase III development and approval, although these companies are no longer distinctively focused on biologic products. (*Clin Ther.* 2021;43:156–171) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: biotechnology, biotechnology company, clinical trials, drug development, initial public offering.

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INTRODUCTION

From its inception in the late 1970s, the biotechnology industry has been portrayed as an engine of innovation for drug discovery and development. The first-generation biotechnology companies promised to develop novel classes of biologic products comprising recombinant proteins, as well as novel applications of molecular technologies to the discovery of conventional small-molecule drugs.

The value proposition of these emerging public companies was that their intellectual property and expertise in recombinant technologies, their association with academic centers and "star" scientists,[1–3] and their ability to enter into multiple partnerships with large pharmaceutical companies for downstream development, manufacturing, and marketing[4,5] would position them to spearhead the translation of these technologies into commercial products. Coupled with the inherent agility of small entrepreneurial companies[6–8] and their ability to access capital from public and private markets,[9] the biotechnology industry was expected to provide a pipeline of innovative products at a time when the pharmaceutical industry was experiencing a productivity crisis.[10,11]

By 1999, one third of new products originated through partnerships between biotechnology and pharmaceutical companies,[12] and the biotechnology sector had established itself as the most productive segment of the biopharmaceutical industry.[7] Munos,[13] examining product approvals from 1950 to 2005, showed that "small companies" contributed to nearly 70% of all product approvals by 2005.

In a landmark study, Pisano[14,15] presented a less sanguine analysis of the performance of the biotechnology industry over its first 25 years (1978–2003). He reported that only a small fraction of public biotechnology companies succeeded in generating significant product revenues or profit. Moreover, he observed that many biotechnology companies were abandoning drug discovery based on recombinant and molecular technologies to focus on in-licensing and development of later-stage projects based on established methods, as well as on repurposing or reformulating existing compounds or new indications.[15] These observations were confirmed by McNamee and Ledley,[16,17] who examined the 10-year performance of 46 companies that completed initial public offerings (IPOs) during the short IPO window in 2000, most of which were focused on applications of genomics. That study found that by 2010, none of those companies had successfully translated genomic technologies or intellectual property into therapeutic products, and that the surviving firms had uniformly pivoted to develop products based on well-established technologies.[16]

The present study characterized late-stage biopharmaceutical development by biotechnology companies that completed IPOs during the 20-year period from 1997 to 2016. This timeframe spanned 5 windows of IPO activity: 1997–1998, 1999–2002, 2003–2007, 2009–2012, and 2013–2016. These companies were public enterprises in an era that spanned significant advances in biomedical science, including: the exponential growth of genomics and codification of various complementary "omics"; the emergence of personalized and precision medicine; the maturation of bioinformatics and health informatics; the discoveries of RNA interference and clustered regularly interspaced short palindromic repeats; dramatic progress in the understanding of stem cells, cancer, and immunology; and significant advances in polymer science, nanotechnology, and formulation. Collectively, these companies raised US $161 billion in private or public investment from founding through the end of 2016 (E. Cleary, L. M. McNamee, S. de Boer, J. Holden, L. Fitzgerald, F. D. Ledley, Comparing long-term value creation after biotech and non-biotech IPOs, 1997–2016, submitted). Like the companies in Pisano's earlier 1978–2003 cohort, these companies typically generated little revenue and consistently had negative profit (losses) while listed on public exchanges, and more than half ended the study period valued below their IPO valuations. Nonetheless, these companies collectively generated hundreds of billions of dollars of growth in both market value and shareholder value, an amount comparable to a control set of paired, nonbiotechnology companies with contemporaneous IPOs (E. Cleary, L. M. McNamee, S. de Boer, J. Holden, L. Fitzgerald, F. D. Ledley, Comparing long-term value creation after biotech and non-biotech IPOs, 1997–2016, submitted).

We asked whether the products developed, at least in part, by these companies successfully advanced to late-stage product development or approval. We asked several specific questions. First, what is the

estimated probability of a company with 1 or more products progressing to Phase III trials or approval in the years after IPO, and what was the timeline for reaching these milestones? We also considered how the estimated probability and timeline of reaching Phase III or approval relate to the status of a company's lead product at IPO, as well as the characteristics of the product in development (small molecule vs biologic; new molecular entity [NME] vs reformulation). Second, what was the role of biotechnology companies in developing these products? Specifically, we asked whether biotechnologies company that initiated development were involved in clinical development, applied for approval from the US Food and Drug Administration (FDA), or developed products with a pharmaceutical partner. Third, using proxy indicators, we explored the importance and innovativeness of the products in these late-stage portfolios, and whether this generation of biotechnology companies continues to fulfill the promise of pioneering important and innovative medicinal products.

MATERIALS AND METHODS

Data Sources

US-based biotechnology companies focused on developing therapeutic products with an IPO date on NASDAQ between January 1, 1997, and December 31, 2016, were identified in the BioCentury BCIQ database. A list of companies included in this study is provided in Supplemental Table S1 (see the online version at https://doi.org/10.1016/j.clinthera.2020.11.012). The IPO windows were modified from those described by Papadopoulos.[18]

For companies with IPOs dated from 2006 to 2016, lead-product status at the time of IPO was identified in BCIQ. For companies with IPOs prior to 2006, lead-product status was determined from S1 filings. Lead-product status was classified as: nothing noted (no mention of a specific product), preclinical, Phase I, Phase II, Phase III, registration, or approved (including marketed).

Products in development by companies in this cohort at any time from 1997 to 2016 were identified in the PharmaProjects database by a search for company name. This search included products initiated by the company, products acquired from other organizations (academic or commercial entities), products that were in preclinical or clinical development by the company at any time, and products that were out-licensed or acquired by another entity. Some products were associated with >1 company. Products were included in this study if Phase III began prior to December 31, 2016, and included those that were in Phase III or approved prior to IPO. A list of products included in this study is provided in Supplemental Table S2. Designations of small molecule versus biologic, as well as NME versus reformulation, was identified in PharmaProjects.

The PharmaProjects database was used to identify clinical status as of December 31, 2016, as either active (the drug was still in development) or discontinued (development was terminated or there was no evidence of ongoing development). The Phase III start date, registration date, and launch date of each product, if given, were identified in PharmaProjects. If no Phase III start date was noted in PharmaProjects, it was estimated to be 45 months prior to registration, based on the mean described by DiMasi et al.[19] If the drug registration year and launch year were equivalent or differed by 1 year, the registration date was considered to be the approval year. If not, the approval year was determined from the FDA website.

An FDA designation of fast track,[20] priority,[21] breakthrough,[22] accelerated,[23] or orphan[24] was identified from fda.gov and FDA annual reports.[25] First-in-class designations were derived from Eder et al[26] or from an updated dataset kindly provided by Dr. Joergen Eder, or were determined using the method described in the article by McGrath et al.[27] The top 200 drugs by sales and prescriptions were also identified from McGrath et al.[27]

Analytical Methods

Kaplan–Meier time-to-event analysis was performed to estimate the probability over time of a company having at least 1 product reach Phase III or approval following IPO. In the Kaplan–Meier analysis, the probability of an event was estimated by the survival function:

$$S(t) = \prod_{i:t_i \le t} \left(1 - \frac{d_i}{n_i}\right), \quad 1$$

where d_i is the number of events happening at time t_i, and n_i is the number of subjects at time t_i. In the present study, d_i is the number of companies that achieved a first Phase III product or first drug approval

at time t_i, and n_i is the number of companies at time $t_i$regardless of whether they had a Phase III product or a drug approval. For each time interval, companies that did not have a Phase III product or drug approval were considered censored and were not included in n_i at time t_i. The estimated probability of a company achieving Phase III product or drug approval since IPO was the multiple of the probabilities at all time intervals. The same method was used for analyzing the estimated probability of companies achieving first product approval, and the estimated probability of a Phase III product reaching product approval. Subset analyses were performed based on the most advanced product status at IPO, IPO window, whether the lead product was an NME or reformulation, and whether the lead product was a biologic or small-molecule drug.

Analyses were performed using IBM SPSS Statistics version 26 (IBM, Armonk, New York), PostgreSQL (PostgreSQL Global Development, Berkeley, California), Excel (Microsoft Corporation, Redmond, Washington), Tableau (Tableau Software, Seattle, Washington), and Python (Python Software Foundation, Beaverton, Oregon).

RESULTS

Biotechnology IPOs 1997 to 2016

From January 1, 1997, through December 31, 2016, 319 biotechnology companies that were focused on developing therapeutic products completed an IPO on NASDAQ. Figure 1 shows the IPO date and lead-product status at IPO for each company in this cohort.

Five windows of heightened IPO activity were evident: 1997–1998, 1999–2002, 2003–2007, 2009–2012, and 2013–2016. This classification differs from previous classifications in that the most recent IPO window was separated into an early window (2009–2012) and a late window (2013–2016). A list of companies included in this study is provided in Supplemental Table S1.

Lead-Product Status at IPO

Of the 319 companies in the present cohort, 40 (13%) described an approved product in the S1 filing

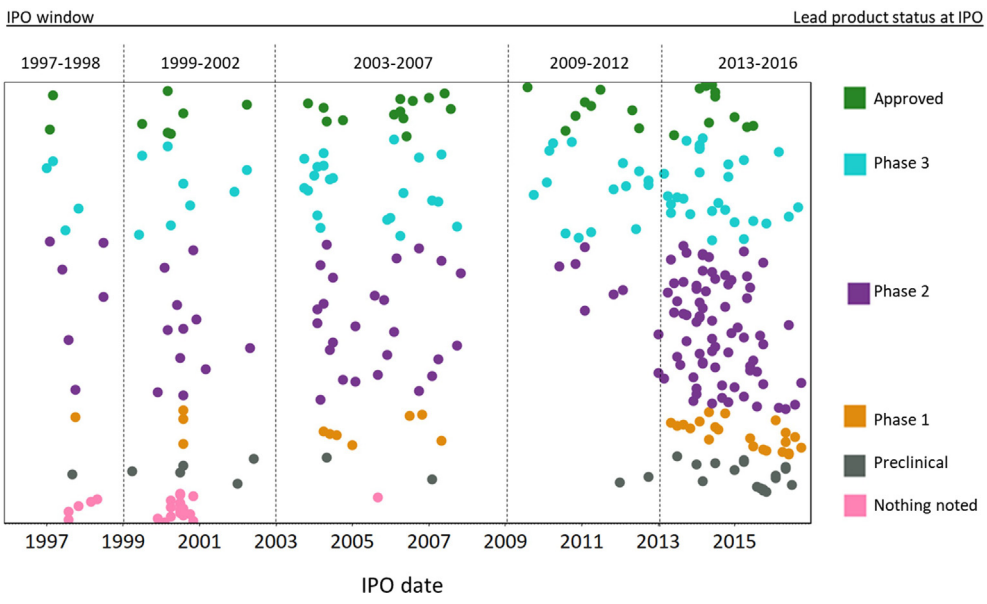

Figure 1. Initial public offering (IPO) dates and lead-product status at IPO for 319 companies focused on developing therapeutic products that completed an IPO from 1997 to 2016. Five windows of IPO activity are distinguished: 1997–1998, 1999–2002, 2003–2007, 2009–2012, and 2013–2016. Lead-product status is classified as: nothing noted (no mention of a specific product), preclinical, Phase I, Phase II, Phase III, or approved.

for their IPO. Another 230 companies (72%) described a product in phased clinical development, including 33 companies (10%) with products in Phase I, 122 companies (38%) with products in Phase II, and 75 companies (24%) with products in Phase III. Of the others, 27 companies (8%) mentioned a product in preclinical development, and 22 (7%) made no mention of products in development (Table I).

The status of the most advanced product at IPO development differed substantially by IPO window (Figure 1 and Table I). Companies in the 2009–2012 window had the highest percentage of products in late-stage development, with 48% having products in Phase III clinical trials and 26% having approved products at the time of IPO. This window came at the end of the 2007–2008 recession, when capital markets remained wary of high-risk investments but were willing to invest in products in late-stage development.[28] In contrast, during the earlier 1999–2002 window, 33% of companies described no products in development. This window spanned the "dot-com bubble" and the completion of the Human Genome Project, and included companies focused on applications of genomics.[16,17]

Late-Stage Product Portfolios, 1997 to 2016

The 319 companies in the cohort were involved in the development of 367 products that reached Phase III or approval during the study period, 1997 to 2016, including 144 products that were approved (Table II). This total included products that were in development by biotechnology companies at any time during the study period, including products that were in-licensed or acquired, products that reached Phase

Table I. Most advanced product status at IPO for biotechnology companies completing an IPO from 1997 to 2016, by IPO window. Data are given as number (%) of IPOs.

IPO Window	No. of IPOs	None	Preclinical	Phase I	Phase II	Phase III	Approved
All (1997–2016)	319	22 (7)	27 (8)	33 (10)	122 (38)	75 (24)	40 (13)
1997–1998	19	5 (26)	1 (5)	1 (5)	6 (32)	4 (21)	2 (11)
1999–2002	49	16 (33)	5 (10)	3 (6)	11 (22)	8 (16)	6 (12)
2003–2007	69	1 (1)	2 (3)	7 (10)	25 (36)	21 (30)	13 (19)
2009–2012	31	0	2 (6)	0	6 (19)	15 (48)	8 (26)
2013–2016	151	0	17 (11)	22 (15)	74 (49)	27 (18)	11 (7)

IPO = initial public offering.

Table II. Number of products in development by biotechnology companies completing an IPO between 1997 and 2016 reaching Phase III or FDA approval by the end of 2016, by approval status. Data are given as number of drug products (% drug type) [% status].

Product Characteristic	All Products	Approved	Active	Discontinued
All	367	144 (39)	158 (43)	65 (18)
Class				
Small molecule	272 (74)	112 (41) [78]	112 (41) [71]	48 (18) [74]
Biologic	95 (26)	32 (34) [22]	46 (48) [29]	17 (18) [26]
FDA category				
NME	236 (64)	78 (33) [54]	112 (47) [71]	46 (19) [71]
Reformulation	131 (36)	66 (50) [46]	46 (35) [29]	19 (15) [29]

FDA = US Food and Drug Administration; IPO = initial public offering; NME = new molecular entity.

III or approval before IPO, as well as products that may have reached Phase III or approval after the product was licensed to another firm or the biotechnology company merged or was acquired by a different firm. This total did not include products that were not in Phase III trials before the end of the study period (December 31, 2016). A list of products included in this study is provided in Supplemental Table S2.

Of the 367 products, 230 (63%) were described in a S1 filing of a company, including 125 (34%) that were in Phase III trials at the time of IPO. Of the 144 approved products, 91 (61%) were described in an S1 filing, including 14 (10%) that were approved before the IPO.

Of the 367 drug products that were in Phase III from 1997 to 2017, 272 were small molecules, and 95 were biologics. These products comprised 236 NMEs and 131 reformulations of existing products. A total of 144 products (39%) were approved before the end of 2016, including 78 of 236 NMEs (33%) and 66 of 131 reformulations (50%). The approved products comprised 112 of 272 small molecules (41%) and 32 of 95 biologics (34%). At the end of the study period, 65 of 367 (18%) products that reached Phase III had been discontinued, and 158 (43%) were still in active development (Tables III and IV).

Timeline and Estimated Probability of Reaching Phase III

As mentioned, Kaplan–Meier time-to-event analysis was used for estimating the probability of a company having 1 or more products advance to Phase III trials or approval after IPO (Figure 2). This method accounted for products that were still in active development at the end of the study period.

Figure 2A shows the estimated probability and timeline for at least 1 product from a company reaching Phase III in the years after IPO. In that analysis, the estimated probability of a company moving at least 1 product into Phase III was 78%, with a median time from IPO to initiation of Phase III of 1 year.

Figure 2B shows the estimated probability and timeline for at least 1 product reaching Phase III in the years after IPO, classified by companies' lead-product status at IPO. Companies with products in Phase II at IPO were most likely to have at least 1 product advance to Phase III (72%), with a median time from IPO to Phase III of 3 years. The estimated probabilities of a product advancing to Phase III were lower for companies with a product in Phase I at IPO (55%) and companies that did not describe products in development at the time of IPO (42%). The median times from IPO to Phase III were 5 years for companies with products in Phase I at IPO and 10 years for companies not describing any products at the time of IPO.

Figure 2C shows the estimated probabilities and timeline for at least 1 product advancing to Phase III in the years after IPO, classified by IPO window. The majority of companies in the 2009–2012 and 2003–2007 windows had products in Phase III at the time of IPO. The estimated probability of companies in

Table III. Contributions of biotechnology companies to products reaching late-stage development (Phase III or approved), by status at the end of the study period (2016). Data are given as number (%) of products unless otherwise specified.

Product Characteristic	All Products (N = 367)	Approved (n = 144)	Active (Phase III) (n = 158)	Discontinued (n = 65)
Company contributions				
Acquired product	14 (4)	4 (3)	6 (4)	4 (6)
Initiated development	275 (75)	99 (69)	127 (80)	49 (75)
Clinical development	357 (97)	137 (95)	156 (99)	64 (98)
FDA submission (% approved)	NA	16 (11)	NA	NA
Developed with pharmaceutical partner	250 (68)	112 (78)	101 (64)	37 (57)

FDA = US Food and Drug Administration; NA = not applicable.

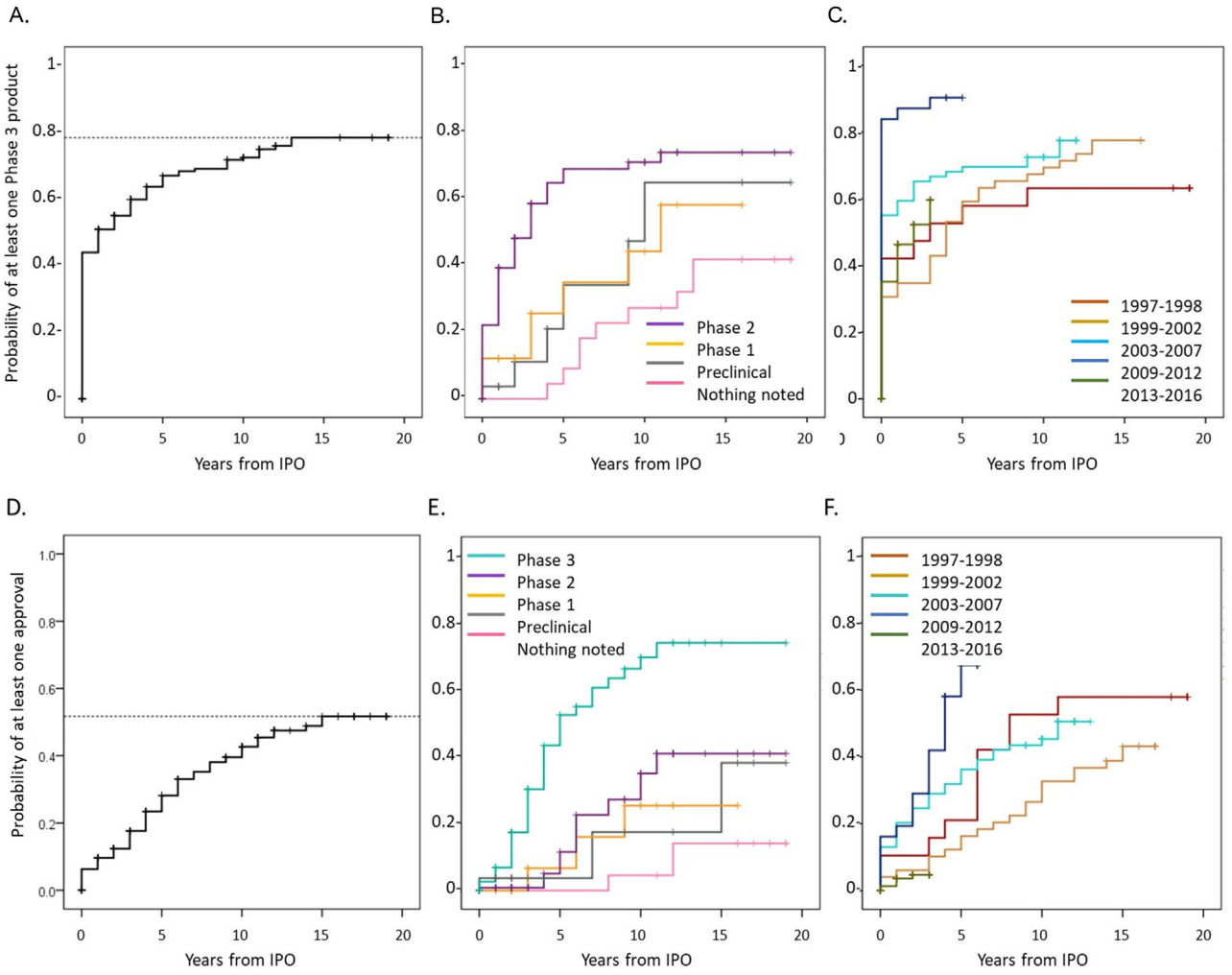

Figure 2. Estimated probabilities (Kaplan–Meier) of a company with an initial public offering (IPO) between 1997 and 2016 having at least 1 product in Phase III trials by the year after IPO, and of a company with an IPO from 1997 to 2016 having at least 1 product approved by the year after IPO. Probabilities were estimated using Kaplan–Meier time-to-event analysis of time elapsed between IPO and first product entering Phase III (A–C), and between IPO and first product receiving approval from the US Food and Drug Administration (D–F). A and D: All companies with IPOs 1997–2016. B and E: Companies classified by lead-product status at IPO (Phase II, Phase I, Preclinical, or Nothing noted). Companies with products in Phase III or approved prior to IPO were not included in this analysis. C and F: Companies classified by IPO window: 1997–1998, 1999–2002, 2003–2007, 2009–2012, or 2013–2016. + = censoring of data (ie, years from IPO at the end of the study period).

the 2009–2012 window having a product in Phase III (94%) was significantly greater than that of companies in other IPO windows. The estimated probability of 1 or more products advancing to Phase III and the median time from IPO to Phase III were similar for companies in other IPO windows. While there were only 3 years of follow-up data for companies in the 2013–2016 window, the time to the median (50% of companies having at least 1 product in Phase III) was not dissimilar to that of other IPO windows.

Timeline and Estimated Probability of Product Approval

As mentioned, Kaplan–Meier time-to-event analysis was also used to estimate the probability and timeline for a company achieving at least 1 FDA product approval in the years after IPO (Figure 2). The estimated probability of at least 1 product approval was 52% (Figure 2D).

Figure 2E shows the estimated probability of at least 1 product from a company being approved in the years after IPO, based on the lead-product status at IPO. This analysis included 27 products that were approved at the time of IPO and 59 products that were in Phase III at the time of IPO. Companies with a product in Phase III at the time of IPO had the highest estimated probability of at least 1 product approval (74%), with a median time from IPO to approval of 5 years. The estimated probability of at least 1 product being approved was lower for companies with products in Phase II at the time of IPO (41%), and the median time from IPO to product approval was longer. The estimated probabilities of approval were substantially lower for companies with products in Phase I at the time of IPO (25%) and for those with no products noted at IPO (14%), and the times from IPO to approval of these products were also longer.

Figure 2F shows the estimated probabilities of at least 1 product being approved, classified by IPO window. Companies in the 2009–2012 window had the highest estimated probability of at least 1 product approval, with a median time from IPO to approval of 4 years. The estimated probability of at least 1 product being approved was lower for each of the other windows, and time from IPO to approval was substantially longer.

The probability of at least 1 product approval was somewhat higher, and the timeline from IPO to first product approval was shorter, for companies developing small molecules rather than biologics (Figure 3A). For approved products, the mean (SD) times from initiation of Phase III trials to approval were 5.03 (2.83) years for biologics and 4.39 (2.06) years for small molecules ($P = 0.16$ [t test]). There were significant differences between the estimated probabilities of a company having at least 1 product being approved and the timelines from IPO to first product approval for NMEs compared to

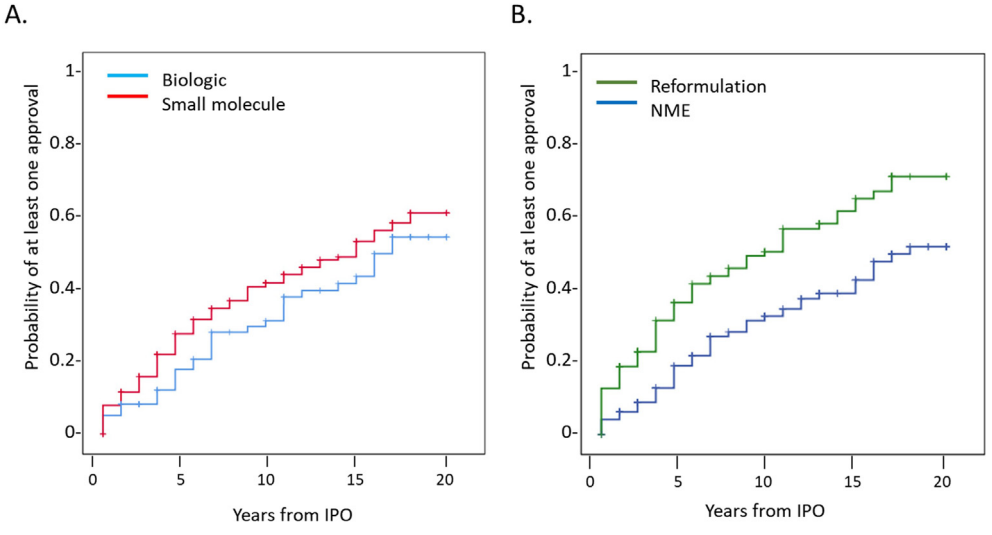

Figure 3. Estimated probability (Kaplan–Meier) of a company with an initial public offering (IPO) from 1997 to 2016 having at least 1 product approved by year after IPO for small molecules versus biologics and new molecular entities (NMEs) versus reformulations. A: Companies classified by molecular class of first approved product (small molecule vs biologic). B: Companies classified by first product being an NME or reformulation. + = censoring of data (ie, years from IPO at the end of the study period).

reformulations, by Kaplan–Meier analysis (both, $P < 0.05$) (Figure 3B). The mean times from initiation of Phase III trials to approval were 4.91 (2.67) years for NMEs and 4.08 (1.55) years for reformulations ($P = 0.03$ [t test]). The significant difference in timelines between NMEs and reformulations was due largely to 8 NMEs with 10 or more years between initiation of Phase III and approval.

Contributions of Biotechnology Companies to Product Development

In the present study, few of the approved products were developed exclusively by biotechnology companies. Companies in this cohort were involved in every stage of initiating development, conducting clinical trials, and regulatory filings for only 8 of 144 approved products (5.6%), and 3 of these products were developed with pharmaceutical partners.

For the other 136 of 144 approved products (94%), the biotechnology companies were involved in some, but not all, aspects of product development (Tables III and IV). Biotechnology companies initiated the development of 275 of 367 products that reached Phase III (75%) and contributed to the clinical development of 357 (97%). Biotechnology companies were involved in FDA submissions for only 16 of 144 approved products (11%). Overall, 250 of 367 development projects (68%) involved pharmaceutical partnerships, including 112 of 144 approved products (78%) and only 37 of 65 discontinued products (57%) (Table III).

Biotechnology companies were more likely to have initiated the development of reformulations than NMEs (85% vs 69%), but less likely to have been involved in FDA submission of applications for these products (9% vs 13%) (Table IV).

Importance and Innovativeness of Products in Late-Stage Development

From 1997 to 2016, companies in the cohort were involved in developing 16% of all NMEs, including 14% of all small molecules and 26% of all biologics (Table V). Over the last 10 years of the study period, 2007–2016, companies in this cohort were involved in developing 17% of all NMEs and 28% of all biologics. Supplemental Fig. S1 shows the percentages of all FDA approvals involving companies in this cohort over time.

Figure 4 shows the therapeutic areas represented by products reaching Phase III, by their status at the end of 2016 (approved, active [still in Phase III], or discontinued), by product type (biologic vs small molecule), and by product type (NME vs reformulation). The largest number of drugs in development and approved were for CNS-related indications, followed by cancer and cardiovascular-related indications. CNS-related indications had the

Table IV. Contributions of biotechnology companies to products reaching late-stage development (Phase III or approved), by characteristic of molecular entity. Data are given as number (%) of products unless otherwise specified.

Product Characteristic	All Products (N = 367)	Small Molecule (n = 272)	Biologic (n = 95)	NME (n = 236)	Reformulation (n = 131)
FDA approved	144 (39)	112 (41)	32 (34)	78 (33)	66 (50)
Company contributions					
Acquired product	14 (4)	11 (4)	3 (3)	10 (4)	4 (3)
Initiated development	275 (75)	205 (75)	70 (74)	164 (69)	111 (85)
Clinical development	357 (97)	267 (98)	90 (95)	226 (96)	131 (100)
FDA submission (% approved)	NA	11/112 (10)	5/32 (16)	10/78 (13)	6/66 (9)
Developed with pharmaceutical partner	250 (68)	189 (69)	61 (64)	179 (76)	71 (54)

FDA = US Food and Drug Administration; NA = not applicable; NME = new molecular entity.

Table V. FDA approvals of NMEs that were in development by companies with IPOs between 1997 and 2016.

Parameter	All NMEs	Small Molecule	Biologic
All FDA approvals, 1997–2016	564	461	103
Companies with IPOs 1997–2016	78	50	28
% FDA approved	16	14	26

FDA = US Food and Drug Administration; IPO = initial public offering; NME = new molecular entity.

highest proportion of small molecules in development, while immunologic and metabolic indications had the highest fraction of biologics. Products for cancer indications had the highest fraction of NMEs compared to reformulations, while CNS-related indications had the highest fraction of reformulations.

Table VI shows proxy measures of the importance and innovativeness of the approved products contributed by these companies. Of the 78 NMEs, 34 (44%) were classified as first-in-class products using the method of Eder et al,[26] which considers a product first in class if it modifies an "unprecedented target or biological pathway."

Table VI also shows the number of expedited designations (accelerated, fast track, breakthrough, priority, or orphan) for approved products. Overall, 57 of 144 approved products (40%) with contributions from these companies had at least 1 expedited designation (mean, 0.81 per product), including 48 of 78 NMEs (62%) (mean, 1.36).

Seven of the products that were in development by the cohort were among the top 200 products by sales in 2016, including sofosbuvir ($4.0 billion), bortezomib ($2.5 billion), omalizumab ($2.3 billion), lisdexamfetamine dimesylate ($2.0 billion), vedolizumab ($1.2 billion), ambrisentan ($0.8 billion), and pirfenidone ($0.8 billion). Two products were among the top 200 by number of prescriptions: lisdexamfetamine dimesylate (11.4 million) and tizanidine (11.1 million).

DISCUSSION

From 1997 to 2016, 319 IPO biotechnology companies that were focused on developing novel biopharmaceutical products completed IPOs. This research examined the likelihood that these newly

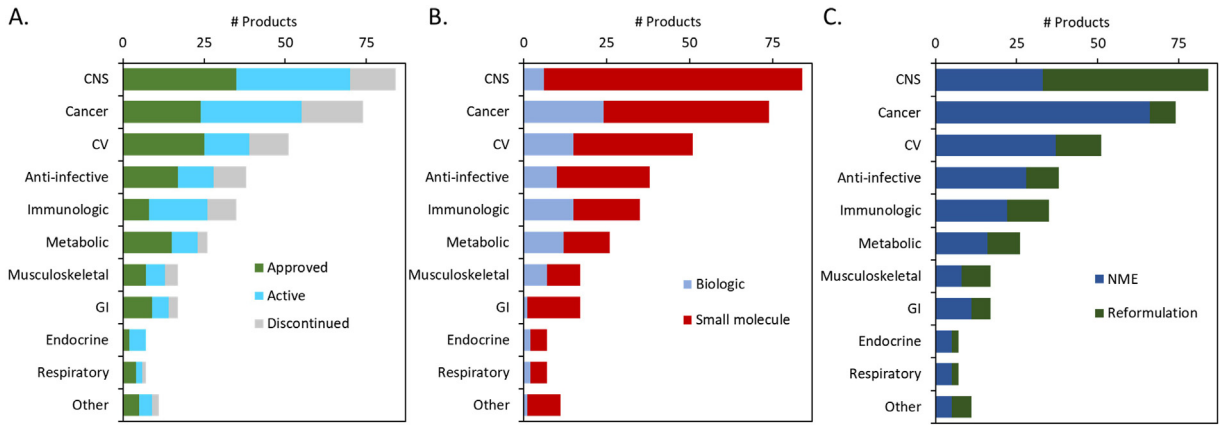

Figure 4. Therapeutic areas of products reaching Phase III development by biotechnology companies with initial public offerings (IPOs) from 1997 to 2016. A: Product status at end of 2016: approved, active (still in Phase III), or discontinued. B: Products by type: biologic or small molecule. C: Products by type: new molecular entity (NME) or reformulation.

Table VI. Characteristics of FDA-approved products in development by biotechnology companies completing IPOs between 1997 and 2016. Data are given as number (%) of products unless otherwise specified.

Product Characteristic	All Products (N = 144)	Small Molecule (n = 111)	Biologic (n = 32)	NME (n = 78)	Reformulation (n = 65)
Sales					
Top 200 by sales	7 (5)	5 (5)	2 (6)	7 (9)	NA
Top 200 by prescription	2 (1)	2 (2)	NA	2 (3)	NA
Expedited-track designation					
Accelerated	13 (9)	10 (9)	3 (9)	12 (15)	1 (2)
Breakthrough	5 (3)	5 (5)	NA	5 (6)	NA
Fast track	20 (14)	13 (12)	7 (22)	20 (26)	NA
Priority	43 (30)	30 (27)	13 (41)	38 (49)	5 (8)
Orphan	35 (24)	21 (19)	14 (44)	31 (40)	4 (6)
At least 1 track	57 (40)	38 (34)	19 (59)	48 (62)	9 (14)
Tracks per product, mean	0.81	0.71	1.16	1.36	0.15
First-in-class NME	—	20/50 (40)	14/28 (50)	34 (44)	—

FDA = US Food and Drug Administration; IPO = initial public offering; NA = not applicable; NME = new molecular entity.

public companies would contribute to products reaching Phase III clinical trials or approval, the timeline for achieving these crucial developmental and business milestones, the role of these companies in the development process, as well as the importance and innovativeness of the products that they developed.

Collectively, the late-stage pipelines of these companies comprised 367 products that were in Phase III trials or approved at some time during the study period. This total includes products initiated by a biotechnology company, products acquired from other academic or corporate entities, products that were subsequently licensed to another entity, and products that were acquired by another entity as a part of a corporate acquisition. It should be emphasized that the present analysis was focused on estimating the probability of a *company* having a product that reached Phase III or approval and the timelines from IPO to approval, not the probability or timeline of any single product reaching these milestones.

With a focus on product approvals, the findings from the present analysis suggest that companies in this cohort had an estimated 52% probability of successfully bringing products to market, with the majority of approvals occurring >5 years after IPO. This estimated probability of a company contributing to at least 1 product approval is substantially higher than the often-quoted probabilities that any single candidate product successfully proceeds through phased clinical trials to approval.[29–32]

As might have been expected, the most important factor in the probability of at least 1 product being approved was the clinical stage of a company's most advanced product at IPO, with >70% of companies with a product in Phase III at the time of IPO having at least 1 approved product, and <40% of companies without a product in Phase III at IPO achieving a product approval. There were significant differences between the IPO windows in the number of companies having products in advanced development and, consequently, the probability. Companies in the 2009–2012, coming at the end of the Great Recession, were most likely to report products in Phase III at the time of IPO and had an estimated probability of at least 1 product being approved of >70%. In contrast, companies in the 1999–2000 window, at the height of the "irrational exuberance" of the dot-com boom, had the fewest products in development and the lowest estimated probability of achieving product approval.

The primary contribution of most companies in this cohort was the initiation of product development. This finding is consistent with the conventional conception of the biotechnology industry as a source of innovation. This finding also suggests that few of the companies completing IPOs between 1997 and 2016 have evolved into fully integrated pharmaceutical companies capable of taking products into development and through regulatory review. In fact, 37% of approved products in this study were approved only after the product was licensed to another firm, or the biotechnology company itself was acquired or merged.

This finding is consistent with the observations that most of these companies had only limited revenue and negative profits (losses) throughout the study period (E. Cleary, L. M. McNamee, S. de Boer, J. Holden, L. Fitzgerald, F. D. Ledley, Comparing long-term value creation after biotech and nonbiotech IPOs, 1997–2016, submitted). By the end of 2016, only 4 companies (United Therapeutics [Silver Spring, Maryland], Jazz Pharmaceuticals [Dublin, Ireland], BioMarin Pharmaceutical [Novato, California], and Horizon Therapeutics [Dublin, Ireland]) had generated >$1 billion in per-annum revenue, and only 1 other company (Acorda Therapeutics [New York, New York]) had >$0.5 billion in revenue. Moreover, 50 of 92 companies with at least 1 approved product were acquired before the end of the study period, 29 of which had market capitalizations of >$1 billion (E. Cleary, L. M. McNamee, S. de Boer, J. Holden, L. Fitzgerald, F. D. Ledley, Comparing long-term value creation after biotech and non-biotech IPOs, 1997–2016, submitted).

The overriding observation from the present study was that the cohort of biotechnology companies with IPOs from 1997 to 2016 is no longer distinctively focused on applications of recombinant or molecular technologies. In fact, 78% of all product approvals associated with these companies were of small molecules and 36% were of reformulations. While these companies were engaged in a broad spectrum of pharmaceutical technologies, they did contribute to a higher percentage of all biologic products approved over this period (28%) than that of small molecules (15%). These data are consistent with the observations of Pisano[15] that the biotechnology industry, as a whole, was moving away from its conventional focus on protein therapeutics as early as 2003.

The growing fraction of small molecules may reflect maturation of research on drug targets discovered through molecular biology and genomics to the point of being able to support drug discovery and development.[33,34] Some of this change, however, may also reflect that companies are pivoting away from the risks of developing products from nascent technologies to focus on applications of older, established methods.[16,17] Some of the apparent change may be semantic, reflecting the evolving definition of a biotechnology company,[35] and reflecting that companies that might have once been categorized as "small pharmaceuticals" are now commonly classified as biotechnology companies.

Considered as a whole, the product portfolios of these emerging, public biotechnology companies do not stand out as particularly innovative or important based on available proxy measures. A somewhat higher percentage of NMEs arising from these companies were classified as first in class (44%)[36] than described previously by Eder et al[26] (34%) for the 324 NMEs approved between 1999 and 2013. The percentage of approved products with at least 1 expedited designation, however, and the mean number of designations for each NME, were not dissimilar from those for all approved products. Kesselheim and Darrow[37] reported that 174 of 312 (56%) of NMEs approved in 2002–2013 benefited from at least 1 accelerated-path designation. In that study, the number of products receiving at least 1 designation each year ranged from 28% in 2001 to >60% in 2013, with the mean numbers of designations/products ranging from 0.6 in 2000 to >1.72 in 2014.[38]

By the end of 2016, 7 of the products developed by these companies had achieved blockbuster status (per-annum sales of >$1 billion). Of these, several were first-in-class products with novel indications, including sofosbuvir,[a] a nucleotide analogue for treating hepatitis C, and omalizumab,[b] a monoclonal antibody against immunoglobulin E used for the

a Sovaldi® (Gilead Sciences, Foster City, California)

b Xolair® (Genentech, South San Francisco, California)

treatment of persistent allergic asthma. Other blockbusters were not first in class using the criteria of Eder et al,[26] but provided enhanced effects or specificities, including ambrisentan,[c] an endothelin inhibitor indicated for the treatment of pulmonary artery hypertension, and vedolizumab,[d] an integrin inhibitor indicated for the treatment of Crohn disease and ulcerative colitis. Some blockbusters, however, were associated with well-established biological targets but offered clinical advantages, including lisdexamfetamine,[e] an amphetamine prodrug indicated for the treatment of attention-deficit/hyperactivity disorder, and tizanidine,[f] an α_2-receptor antagonist indicated for the treatment of muscle spasticity related to multiple sclerosis or spinal cord injury.

Other approved drugs that represented significant innovations were selinexor,[g] the first selective inhibitor of nuclear export for treating multiple myeloma; 3 poly−ADP ribose polymerase inhibitors (talazoparib,[h] rucaparib,[i] and niraparib[j]), as well as a number of enzyme-replacement therapies for the treatment of previously untreatable genetic diseases (elosulfase alfa,[k] for treating Morquio syndrome; laronidase,[l] for treating mucopolysaccharidosis type 1; and galsulfase,[m] for treating mucopolysaccharidosis type 4).

c Letairis® (Gilead)

d Entyvio® (Millennium Pharmaceuticals, Cambridge, Massachusetts)

e Vyvanse® (Takeda Pharmaceutical Company, Tokyo, Japan)

f Zanaflex® (Acorda Therapeutics, Ardsley, New York)

g Xpivio® (Karyopharm Therapeutics Inc, Newton, Massachusetts)

h Talzenna® (Pfizer Oncology, New York, New York)

i Rubraca® (Clovis Oncology, Boulder, Colorado)

j Zejula® (GlaxoSmithKline, Research Triangle Park, North Carolina)

k Vimizim® (BioMarin Pharmaceutical, Novato, California)

l Aldurazyme® (Genzyme, Cambridge, Massachusetts)

m Naglazyme® (BioMarin)

The dataset of products reaching Phase III trials contained many state-of-the-art products, including 20 candidate tyrosine kinase inhibitors with individual specificities and an array of monoclonal antibodies targeted against various immune modulators. In contrast, there were 17 products comprising opioid agonists or antagonists (including 6 reformulations of oxycodone) for the treatment of pain, opioid addiction, or gastric hypermobility, as well as many reformulations of NSAIDs, corticosteroids, antifungals, and antibiotics.

There are no generally accepted metrics for use in measuring the innovativeness and importance of novel biopharmaceutical products.[38] The definition of *first in class* used in this analysis refers explicitly to the first drug against a particular target,[26] and does not address novel mechanisms of action, drug classes, or clinical indications.[39,40] The significance of expedited designations as a proxy for innovation or importance is unclear. Chambers et al[41] reported that drugs receiving at least 1 expedited review designation provide greater health gains (measured in quality-adjusted life-years) than other products. Nonetheless, concern has also been expressed that the reduced timelines afforded to products with expedited designations may lead to results that are not confirmed by robust follow-up studies[42] and that data on drug tolerability may not be complete.[43] Finally, data on sales and prescriptions, while reflecting prescribing practices, also reflect drug pricing, the prevalence of disease, marketing, and market share rather than the impact and innovativeness of a product. Future research, facilitated by continuing advances in cost-effectiveness analysis or other methods,[39,40,44–46] would be required for a more full assessment of the clinical significance of products produced by these companies.

Study Limitations

There were several limitations in the present study. First, this study was focused explicitly on companies that had IPOs in the 20-year period from 1997 to 2016, and did not describe the broader, public biotechnology sector. Specifically, this dataset did not include products developed by surviving companies from the first wave of biotechnology IPOs described by Pisano,[15] such as Amgen (Thousand Oaks, California) and Biogen (Cambridge, Massachusetts),

nor companies in the 1991–1994 IPO window, which spawned a remarkable number of successful companies, including Alkermes (Dublin, Ireland), Alnylam Pharmaceuticals (Cambridge, Massachusetts), Gilead Sciences (Foster City, California), Isis (Ionis Pharmaceuticals; Carlsbad, California), and Vertex Pharmaceuticals (Boston, Massachusetts).[47] This study also did not take into account products in development by private companies that may have been acquired or failed without listing their stock on public exchanges.

Second, the dataset contained a disproportionate number of companies from the current IPO window, which began in 2013. These companies had <5 years of follow-up at the end of the study period, and the analysis did not include products that may have proceeded to Phase III or approval after this date. This limitation was addressed in the statistical analysis using the Kaplan–Meier time-to-event analysis, which takes into account censoring of data. This method is commonly used in clinical trials in which not all study subjects may have reached the clinical end point of a study by the end of the study period.[48] It should be noted, however, that the Kaplan–Meier method is predicated on the assumption that the characteristics of the study population remain statistically similar through the study period. In fact, our data show significant variation in the success rates in different IPO windows, notably the 2009–2012 window, when the percentage of companies with products in Phase III was significantly higher. Ultimately, the probabilities calculated by Kaplan–Meier can be only confirmed or refuted by retrospective analysis over the next several decades as companies in the current IPO window and their products mature.

CONCLUSIONS

The present study demonstrates that biotechnology companies completing an IPO between 1997 and 2016 made substantive contributions to new product development, and that the majority of companies will contribute to developing a product that reaches Phase III trials and approval. The findings from this work also suggest that emerging public biotechnology companies are no longer distinctively focused on developing biologic products.

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AUTHOR CONTRIBUTIONS

Conceptualization and validation were provided by L.M., E.C., and F.L.. Methodology and formal analysis were provided by L.M., S.Z., E.C., and F.L. Investigation was provided by L.M., S.Z., U.S., E.C., and F.L. Resources, data curation, and writing (review and editing) were provided by E.C. and F.L. Writing (drafting) was provided by S.Z. and F.L. Visualization was provided by Z.S., E.C., and F.L. Supervision, project administration, and funding acquisition were provided by F.L.

DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

DATA AND MATERIALS AVAILABILITY

The data from this study are freely available on scholar@bentley (scholar.bentley.edu), part of the Digital Commons (bpress.com) platform.

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SUPPLEMENTAL MATERIAL

Table S1. Biotechnology companies in study cohort; companies focused on therapeutic development with IPOs between January 1, 1997 and December 31, 2016.

Company name	IPO date	# phase 3	# approvals
Aastrom Biosciences Inc.	1997	3	2
Abgenix Inc.	1998	3	1
Acadia Pharmaceuticals Inc.	2004	0	1
Acceleron Pharma Inc.	2013	1	0
AcelRx Pharmaceuticals Inc.	2011	1	1
Achaogen Inc.	2014	1	0
Acorda Therapeutics Inc.	2006	2	3
Adamas Pharmaceuticals Inc.	2014	1	1
ADMA Biologics Inc.	2013	1	0
Adolor Corp.	2000	1	1
Aegerion Pharmaceuticals Inc.	2010	0	2
Aerie Pharmaceuticals Inc.	2013	2	0
Agile Therapeutics Inc.	2014	1	0
Agios Pharmaceuticals Inc.	2013	1	0
Aimmune Therapeutics, Inc.	2015	1	0
Akebia Therapeutics Inc.	2014	1	0
Alder Biopharmaceuticals Inc.	2014	1	0
Alexza Pharmaceuticals Inc.	2006	0	1
Alimera Sciences Inc.	2010	0	1
Allos Therapeutics Inc.	2000	1	1
Alnylam Pharmaceuticals Inc.	2004	2	0
Ambit Biosciences Corp.	2013	1	0
Amicus Therapeutics Inc.	2007	2	0
Anacor Pharmaceuticals Inc.	2010	1	1
Anthera Pharmaceuticals Inc.	2010	3	0
Antigenics Inc.	2000	3	0
Ardelyx Inc.	2014	1	0
Arena Pharmaceuticals Inc.	2000	0	2
Argos Therapeutics Inc.	2014	1	0
Array BioPharma Inc.	2000	4	0
Auspex Pharmaceuticals Inc.	2014	1	0
Auxilium Pharmaceuticals Inc.	2004	0	1
Aveo Pharmaceuticals Inc.	2010	1	0
Axsome Therapeutics, Inc.	2015	2	0
Barrier Therapeutics Inc.	2004	2	3
Biodel Inc.	2007	1	0
BioDelivery Sciences International Inc.	2002	2	3
BioMarin	1999	6	4
BioMimetic Therapeutics Inc.	2006	1	1

Table S1. (*Continued*)

Company name	IPO date	# phase 3	# approvals
Biopure	1999	1	0
bluebird bio Inc.	2013	1	0
Cadence Pharmaceuticals Inc.	2006	1	1
CancerVax Corp.	2003	1	0
Cara Therapeutics Inc.	2014	1	0
Carbylan Therapeutics Inc.	2015	4	0
Catalyst Pharmaceutical Partners Inc.	2006	1	0
Cell Therapeutics Inc.	1997	3	1
Cempra Inc.	2012	1	0
ChemoCentryx Inc.	2012	1	0
Chiasma Inc.	2015	1	0
Chimerix Inc.	2013	1	0
Clearside Biomedical Inc.	2016	1	0
Clovis Oncology Inc.	2011	1	1
Coherus BioSciences Inc.	2014	2	0
Coley Pharmaceutical Group Inc.	2005	1	0
Collegium Pharmaceutical Inc.	2015	0	1
CoLucid Pharmaceuticals Inc.	2015	1	0
Conatus Pharmaceuticals Inc.	2013	1	0
Concert Pharmaceuticals Inc.	2014	1	0
Corcept Therapeutics Inc.	2004	0	1
Corgentech Inc.	2004	2	1
Corixa Corp.	1997	1	1
CoTherix Inc.	2004	0	1
Coulter Pharmaceutical Inc	1997	0	1
Critical Therapeutics Inc.	2004	0	2
Cumberland Pharmaceuticals Inc.	2009	1	3
Cytokinetics Inc.	2004	1	0
deCode genetics Inc.	2000	1	0
Dendreon Corp.	2000	0	1
Depomed Inc.	1997	0	3
Dermira Inc.	2014	2	0
Dipexium Pharmaceuticals Inc.	2014	1	0
Dov Pharmaceutical Inc.	2002	4	0
Durata Therapeutics Inc.	2012	0	1
Dyax Corp.	2000	1	3
Dynavax Technologies Corp.	2004	2	0
Eagle Pharmaceuticals Inc.	2014	2	3
Edge Therapeutics	2015	1	0
Egalet Corp.	2014	2	0
Eleven Biotherapeutics Inc.	2014	1	0
Enanta Pharmaceuticals Inc.	2013	1	0
Endocyte Inc.	2011	1	0

(*continued on next page*)

Table S1. (*Continued*)

Company name	IPO date	# phase 3	# approvals
Esperion Therapeutics Inc.	2013	1	0
Evoke Pharma Inc.	2013	1	0
Exelixis Inc.	2000	2	2
Eyetech Pharmaceuticals Inc.	2004	0	1
FibroGen Inc.	2014	1	0
Flexion Therapeutics Inc.	2014	1	0
GlycoMimetics Inc.	2014	1	0
GTx Inc.	2004	2	0
Horizon Pharma Inc.	2011	0	2
Hyperion Therapeutics Inc.	2012	0	1
Idenix Pharmaceuticals Inc.	2004	0	1
Ilex Oncology Inc.	1997	2	2
Immtech Pharmaceuticals Inc.	1999	1	0
Inhibitex Inc.	2004	3	0
Inotek Pharmaceuticals Corp.	2015	2	0
Inspire Pharmaceuticals Inc.	2000	3	0
Intercept Pharmaceuticals Inc.	2012	0	1
InterMune Inc.	2000	0	1
Intersect ENT Inc.	2014	1	0
IntraBiotics Pharmaceuticals Inc.	2000	1	0
Ironwood Pharmaceuticals Inc.	2010	0	1
Ista Pharmaceuticals Inc.	2000	3	3
Jazz Pharmaceuticals Inc.	2007	2	3
Karyopharm Therapeutics Inc.	2013	1	0
KemPharm Inc.	2015	1	0
Keryx Biopharmaceuticals Inc.	2000	0	1
Kos Pharmaceuticals Inc.	1997	1	5
Kosan Biosciences Inc.	2000	1	0
Kythera Biopharmaceuticals Inc.	2012	0	1
LeukoSite Inc.	1997	0	2
Lexicon Pharmaceuticals Inc.	2000	2	0
MacroGenics Inc.	2013	2	0
MannKind Corp.	2004	0	1
Map Pharmaceuticals Inc.	2007	2	0
Marshall Edwards Inc.	2002	1	0
Maxygen Inc.	1999	1	0
Merrimack Pharmaceuticals Inc.	2012	1	1
Momenta Pharmaceuticals Inc.	2004	1	0
Myogen Inc.	2003	2	1
Neothetics Inc.	2014	1	0
New River Pharmaceuticals Inc.	2004	0	1
NewLink Genetics Corp.	2011	3	0
NitroMed Inc.	2003	0	1
Northwest Biotherapeutics Inc.	2001	2	0

Table S1. (*Continued*)

Company name	IPO date	# phase 3	# approvals
Novacea	2006	2	0
Novan Inc.	2016	1	0
NuPathe Inc.	2010	0	1
Ocular Therapeutix Inc.	2014	1	0
Oculus Innovative Sciences Inc.	2007	0	1
Omeros Corp.	2009	2	1
Omrix Biopharmaceuticals Inc.	2006	1	2
Omthera Pharmaceuticals Inc.	2013	0	1
Oncobiologics Inc.	2016	1	0
Onconova Therapeutics Inc.	2013	1	0
Ophthotech Corp.	2013	1	0
Optimer Pharmaceuticals Inc.	2007	1	1
OraPharma Inc.	2000	0	1
Orexigen Therapeutics Inc.	2007	0	1
Osiris Therapeutics Inc.	2006	1	1
Otonomy Inc.	2014	1	1
Pacira Pharmaceuticals Inc.	2011	0	3
Pain Therapeutics Inc.	2000	3	0
Pharmasset Inc.	2007	1	1
Pharmion Corp.	2003	0	1
Portola Pharmaceuticals Inc.	2013	2	0
Pozen Inc.	2000	2	4
Praecis Pharmaceuticals Inc.	2000	0	1
Progenics Pharmaceuticals Inc.	1997	3	1
Proteon Therapeutics Inc.	2014	1	0
PTC Therapeutics	2013	1	0
Radius Health Inc.	2014	1	0
Reata Pharmaceuticals Inc.	2016	1	0
Receptos Inc.	2013	1	0
Recro Pharma Inc.	2014	1	0
Relypsa Inc.	2013	0	1
Renovis Inc.	2004	1	0
Replidyne Inc.	2006	1	0
Revance Therapeutics Inc.	2014	1	0
Ribapharm Inc.	2002	1	1
Rigel Pharmaceuticals Inc.	2000	2	0
Ritter Pharmaceuticals Inc.	2015	1	0
Sage Therapeutics Inc.	2014	1	0
Santarus Inc.	2004	1	4
Seattle Genetics Inc.	2001	0	1
Seres Therapeutics Inc.	2015	1	0
SGX Pharmaceuticals	2006	1	0
Somaxon Pharmaceuticals Inc.	2005	0	1

(*continued on next page*)

Table S1. (*Continued*)

Company name	IPO date	# phase 3	# approvals
Spark Therapeutics Inc.	2015	1	0
Sucampo Pharmaceuticals Inc.	2007	0	1
Sunesis Pharmaceuticals Inc.	2005	1	1
Supernus Pharmaceuticals Inc.	2012	2	3
Syndax Pharmaceuticals Inc.	2016	1	0
Synta Pharmaceuticals Corp.	2007	1	0
Tanox Inc.	2000	2	1
Targacept Inc.	2006	0	1
Targanta Therapeutics Corp.	2007	0	1
Telik Inc.	2000	1	0
Tercica Inc.	2004	0	1
Tesaro Inc.	2012	1	1
Tetraphase Pharmaceuticals Inc.	2013	1	0
The Medicines Co.	2000	0	2
Theravance Inc.	2004	1	1
Threshold Pharmaceuticals Inc.	2005	2	0
Tokai Pharmaceuticals Inc.	2014	1	0
Transcend Therapeutics Inc.	1997	1	0
Tranzyme Inc.	2011	1	0
Trevena Inc.	2014	1	0
Trimeris Inc.	1997	0	1
Trius Therapeutics Inc.	2010	0	1
Tularik Inc.	1999	1	0
Ultragenyx Pharmaceutical Inc.	2014	3	0
United Therapeutics Corp.	1999	1	3
Vanda Pharmaceuticals Inc.	2006	0	2
Ventrus Biosciences Inc.	2010	2	0
Versartis Inc.	2014	1	0
Versicor Inc.	2000	0	2
vTv Therapeutics Inc.	2015	1	0
XBiotech Inc.	2015	1	0
Zafgen Inc.	2014	1	0
Zogenix Inc.	2010	1	3
ZS Pharma Inc.	2014	1	0
ZymoGenetics Inc.	2002	1	5

Table S2. Products in development by companies in study cohort that reached phase 3 development 1997–2016.

Generic Drug Name	Brand name	Approval year
bone marrow ther		
bone progenitor cell		
cord blood ther		
autologous cultured chondrocytes	Carticel	1995
matrix-induced autologous chondrocyte implantation	Carticel	2012
gavilimomab		
patritumab		
tremelimumab		
panitumumab	Vectibix	2006
pimavanserin tartrate	Nuplazid	2015
luspatercept	Reblozyl	
sufentanil	Zalviso	2015
sufentanil	Dsuvia	
plazomicin	Zemdri	
diazepam	Plumia	
levodopa	Inbrija	
tizanidine	Zanaflex	1997
capsaicin	Qutenza	2009
dalfampridine	Ampyra	2010
amantadine	Gocovri	
donepezil + memantine	Namzaric	2014
RI-002	Asceniv	
bevenopran		
alvimopan	Entereg	2008
lomitapide	Juxtapid	2012
metreleptin	Mylept	2014
AR-13324 + latanoprost	Roclatan	
netarsudil	Rhopressa	
ethinylestradiol + levonorgestrel	Twirla	
enasidenib	Idhifa	
vadadustat		
eptinezumab	Vyepti	
loxapine	Adasuve	2012
fluocinolone acetonide	Lluvien	2014
efaproxiral	Efaproxyn	
pralatrexate	Folotyn	2009
Patisiran	Onpattro	
revusiran		
quizartinib	Xospata	
migalastat	Galafold	
allantoin	Alwextin	
crisaborole	Eucrisa	

(*continued on next page*)

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
tavaborole	Kerydin	2014
blisibimod		
liprotamase	Sollpura	
varespladib		
HIV vaccine		
QS-21		
vitespen	vitespen	
tenapanor hydrochloride	Ibsrela	
lorcaserin hydrochloride, extended release	Belviq XR	2016
lorcaserin hydrochloride	Belviq	2012
rocapuldencel T		
binimetinib	Mektovi	
encorafenib	Brafovi	
filanesib		
selumetinib		
deuterated tetrabenazine	Austedo	2017
collagenase Clostridium histolyticum	Xiaflex	2009
tivozanib	Fotivda	
ketoconazole + desonide	Seboride	
liarozole		
itraconazole	Sporanox	2010
ketoconazole	Xolegel	2006
miconazole	Vusion	2006
insulin, ultra-rapid-acting	Linjeta	
amphotericin B-2		
clonidine, topical		
buprenorphine + naloxone	Bunavail	2014
buprenorphine, BEMA film (low dose)	Belbuca	2015
fentanyl, Meda	Onsolis	2009
drisapersen	Kyndrisa	
heparinase I	Neutralase	
pegvaliase	Palynziq	
reveglucosidase alfa		
talazoparib	Talenna	
amifampridine	Firdapse	
elosulfase alfa	Vimizim	2014
Galsulfase	Naglazyme	2005
laronidase	Aldurazyme	2003
sapropterin dihydrochloride	Kuvan	2007
becaplermin + β-tricalcium phosphate-3	Regranex	
becaplermin + β-tricalcium phosphate-1	Regranex*	2005
haemoglobin, OPK Biotech	hemopure	
adrenoleukodystrophy therapy		
omiganan pentahydrochloride		

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
paracetamol	Ofirmev	2010
cancer vaccine	Canvaxin	
difelikefalin		
hyaluronan + triamcinolone		
hyaluronan	ActaVisc	
hyaluronic acid + corticosteroid	Hydros	
hyaluronic acid	ActraVisc	
paclitaxel polyglumex	Opaxio	
pacritinib	Empaxiq	
pixantrone	Pixuvri	
arsenic trioxide	Trisenox	2000
solithromycin	Solithera	
vercirnon	Traficet	
octreotide	Mycapssa	
brincidofovir		
rociletinib		
rucaparib	Rubraca	2016
etanercept		
adalimumab		
PF-676		
oxycodone	Xtampza	2016
lasmiditan	Reyvow	
emricasan		
deuterated dextromethorphan + quinidine		
mifepristone	Korlym	2012
capsaicin	Adlea	
edifoligide		
lidocaine	Zingo	2007
melanoma vaccine		
131I-tositumomab	Bexxar	2003
iloprost trometamol	Ventavis	2005
zileuton	Zyflo	1997
zileuton	Zyflo CR	2007
acetylcysteine	Acetadote	
acetylcysteine	Acetadote	2011
ibuprofen	Caldolor	2009
omeprazole + clarithromycin + amoxicillin	Omeclamox	2014
tirasemtiv		
veliflapon		
sipuleucel-T	Provenge	2010
ciprofloxacin	Proquin XR	2005
gabapentin	Gralise	2011
metformin	Glumetza	2005

(*continued on next page*)

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
certolizumab	Cimza	
glycopyrronium	Qbrexza	
pexiganan	Locilex	
amitifadine		
bicifadine		
indiplon		
ocinaplon		
dalbavancin	Dalvance	2014
lanadelumab	Takhzyro	
ecallantide	Kalbitor	2009
necitumumab	Portrazza	2015
ramucirumab	Cyramza	2014
Tolamba	Tolamba	
hepatitis-B vaccine + 1018-ISS	Heplisav-B	2017
bivalirudin	Kangio	
IG-002		
argatroban	Argatroban	2011
bendamustine	Bendeka	2015
dantrolene sodium	Ryanodex	2014
oxycodone	Oxaydo	
morphine	Arymo	2017
isunakinra	Isunakinra	
paritaprevir	Viekira Pak	
vintafolide	Vynfinit	
bempedoic acid	Nexletol	
metoclopramide	Gimoti	
becatecarin		
esaxerenone	Minnebro	
cabozantinib	Cabometyx	2012
cobimetinib	Cotellic	2015
pegaptanib	Macugen	2004
roxadustat		
triamcinolone	Zilretta	
rivipansel sodium		
enobosarm		
toremifene citrate		
Fareston		
ibuprofen + famotidine	Duexis	2011
prednisone	Rayos	2012
glycerol phenylbutyrate	Ravicti	2013
telbivudine	Tyzeka	2006
crisnatol mesylate		
eflornithine	Vaniqa	
alemtuzumab	Lemtrada	2001

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
clofarabine	Clolar	2004
pafuramidine		
valnivudine		
SA-IGIV		
Veronate		
INO-1001	Pardex	
trabodenoson		
denufosol tetrasodium, Intrana		
denufosol tetrasodium, resp		
diquafosol tetrasodium	Proclaria	
obeticholic acid	Ocaliva	2016
pirfenidone	Esbriet	2014
mometasone furoate stent, Intersect	Propel	
iseganan hydrochloride		
linaclotide acetate	Linzess	2012
aminocaproic acid	Caprogel	
bromfenac (low concentration)	Remura	
prednisolone + tobramycin		
bromfenac	Bromday	2010
hyaluronidase	Hylenex	2005
solriamfetol	Sunosi	2019
alprazolam	Niravam	
sodium oxybate	Xyrem	2002
crisantaspase	Erwinase	2011
Sm153 lexidronam	Quadramet	1997
selinexor	Xpovio	2019
acetaminophen + benzhydrocodone		
ferric citrate	Nephoxil	2015
icatibant	Firazyr	2011
nicotinic acid		
eprosartan mesylate	Teveten	1999
eprosartan mesylate + HCTZ	Teveten	2001
niacin + lovastatin	Advicor	2001
nicotinic acid	Niaspan	1997
tanespimycin		
deoxycholic acid	Kybella	2015
bortezomib	Velcade	2003
vedolizumab	Entyvio	2013
sotagliflozin (oral solution)	Zynquista	
telotristat	Xermelo	2017
margetuximab		
teplizumab		
insulin, Technosphere	Afrezza	2014

(*continued on next page*)

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
budesonide		
dihydroergotamine mesylate		
idronoxil		
somavaratan		
Factor VIIa		
doxorubicin		
irinotecan	Onivyde	2015
adalimumab		
darusentan		
ambrisentan	Letairis	2007
enoximone	Perfan	
salmeterol xinafoate		
lisdexamfetamine dimesylate	Vyvanse	2007
algenpantucel-L		
Ebola vaccine		
turgenpumatucel-L		
isosorbide dinitrate/hydralazine	BiDil	2005
DCVax-Brain		
DCVax-prostate		
vinorelbine, oral		
calcitriol, Transcept		
sumatriptan succinate	Zecuity	2013
dexamethasone		
oxychlorine compounds	Microcyn	2008
ketoprofen + amitriptyline + oxymetazoline		
narsoplimab		
ketorolac + phenylephrine	Omidria	2014
West Nile virus		
fibrin pad	Evarrest	2012
thrombin, topical	Evithrom	2007
EPA + DHA	Epanova	2014
Novonex		
pegpleranib	Fostiva	
fidaxomicin	Dificid	2011
minocycline	Arestin	2001
bupropion + naltrexone	Contrave	2014
remestemcel-L		
OTI-050 (stem cell)		
dexamethasone		
ciprofloxacin	Otripio	2015
morphine, DepoFoam	DepoDur	2004
bupivacaine, DepoFoamdep	Exparel	2011
cytarabine, DepoFoam	Depocyt	1997
naltrexone		

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
oxycodone + naltrexone		
oxycodone, long-acting		
clevudine		
sofosbuvir	Sovaldi	2013
5-azacitidine	Vidaza	2004
andexanet alfa	Andexxa	2018
betrixaban	Bevyxxa	2017
dihydroergotamine mesylate		
naproxen + omeprazole		
metoclopramide + naproxen		2005
aspirin (325 mg) + omeprazole	Yosprala	2016
naproxen + esomeprazole	Vimovo	2010
naproxen + sumatriptan	Treximet	2008
abarelix	Plenaxis	2003
GMK		
leronlimab		
methylnaltrexone	Relistor	2008
vonapanitase		
ataluren		
abaloparatide	Tymlos	2017
ozanimod	Zeposia	2020
meloxicam	Anjeso	2029
patiromer	Veltassa	2015
disufenton		
faropenem medoxomil		
botulinum toxin type A		
tiazofurin		
alpha-interferon + ribavirin	Rebetol	1998
fostamatinib	Tavalisse	2018
R-112		
RP-G28		
brexanolone		
Zulresso	2019	
rifamycin SV	Aemcolo	2018
budesonide	Uceris	2013
conestat alfa	Ruconest	2014
omeprazole, powder	Zegerid	2004
omeprazole, solid	Zegerid	2006
b-vedotin	Adcetris	2011
SER-109		
troxacitabine	Troxatyl	
doxepin	Silenor	2010
voretigene neparvovec		2017

(*continued on next page*)

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
lubiprostone	Amitiza	2006
vosaroxin	Qinprezo	
lifitegrast	Xiidra	2016
molindone		
viloxazine ER		
oxcarbazepine	Oxtellar XR	2012
topiramate, once-daily	Trokendi XR	2013
trospium chloride extended release	Sanctura XR	2007
ganetespib		
lampalizumab		
lebrikizumab		
omalizumab	Xolair	2003
mecamylamine	Inversine	1998
oritavancin	Orbactiv	2014
canfosfamide		
somatomedin-1		2005
niraparib	Zejula	2017
rolapitant	Varubi	2015
eravacycline		
bivalirudin	Angiomax	2000
cangrelor tetrasodium	Kengreal	2015
revefenacin	Yupelri	2018
telavancin	Vibativ	2009
evofosfamide		
glufosfamide		
galeterone		
Procysteine		
ulimorelin		
oliceridine		
enfuvirtide	Fuzeon	2003
tedizolid	Sivextro	2014
batabulin sodium		
aceneuramic acid		
burosumab	Crysvita	2018
vestronidase alfa	Mepsevii	2017
dinutuximab	Unituxin	2015
treprostinil	Orenitram	2013
treprostinil (inhaled)	Tyvaso	2009
beraprost		
iloperidone	Fanapt	2009
tasimelteon	Hetlioz	2014
diltiazem		
iferanserin		
anidulafungin	Eraxis	2006

Table S2. (*Continued*)

Generic Drug Name	Brand name	Approval year
bermekimab	Xilonex	
beloranib		
fenfluramine		
hydrocodone	Zohydro ER	2015
hydrocodone	Zohydro	2013
sumatriptan	Sumavel	2009
sodium zirconium cyclosilicate	Lokelma	2018
BMS-914143		
catridecacog	Tretten	2013
eptacog alfa (activated)	NovoSeven	1999
glucagon		1998
thrombin alfa	Recothrom	2008
azeliragon		
AR-101		
nimodipine		
zoledronic acid		
bupropion + dextromethorphan		
entinostat		
bevacizumab		
bardoxolone methyl		
Zuprata		
NVN-1000		

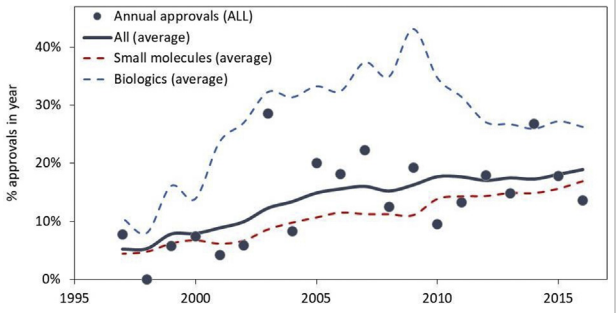

Figure S1. Fraction of annual FDA approvals developed with contributions from biotechnology companies with IPOs from 1997 to 2016. Annual data is indicated by symbols. The 7-year moving average for all approvals is shown as a solid line. The 7-year moving average for the fraction of biological products is shown as a dashed blue line. The 7-year moving average for the fraction of small molecules is shown as a dashed orange line.