Public sector financial support for late stage discovery of new drugs in the United States: cohort study

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ABSTRACT

OBJECTIVE

To determine the extent to which late stage development of new drugs relies on support from public funding.

DESIGN

Cohort study.

SETTING

All new drugs containing one or more new molecular entities approved by the US Food and Drug Administration (FDA) between January 2008 and December 2017 via the new drug application pathway.

MAIN OUTCOME MEASURES

Patents or drug development histories documenting late stage research contributions by a public sector research institution or a spin-off company, as well as each drug's regulatory approval pathway and first-in-class designation.

RESULTS

Over the 10 year study period, the FDA approved 248 drugs containing one or more new molecular entities. Of these drugs, 48 (19%) had origins in publicly supported research and development and 14 (6%) originated in companies spun off from a publicly supported research program. Drugs in these groups were more likely to receive expedited FDA approval (68% *v* 47%, P=0.005) or be designated first in class (45% *v* 26%, P=0.007), indicating therapeutic importance.

CONCLUSIONS

A review of the patents associated with new drugs approved over the past decade indicates that publicly supported research had a major role in the late stage development of at least one in four new drugs, either through direct funding of late stage research or through spin-off companies created from public sector research institutions. These findings could have implications for policy makers in determining fair prices and revenue flows for these products.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Publicly sponsored research has a substantial role in the upstream, basic science investigations behind most new drugs

About 14% of new molecular entities approved in 1990-2007 had late stage, patentable contributions from a public sector research institution

WHAT THIS STUDY ADDS

Among 248 new small molecule drugs approved by the US Food and Drug Administration in 2008-17 containing a new molecular entity, 25% had key late stage research contributions from public sector research institutions (19%) or spin-off companies from one of these institutions (6%), often with key patents on the drug credited in part to these institutions

These publicly sponsored drugs were more likely to receive expedited regulatory designation and be first in class, suggesting high therapeutic importance

Publicly sponsored research has a substantial and growing role in late stage drug discovery and development, and this information can inform policies related to drug pricing and fair compensation for public sector investment.

Introduction

Public sector support funds much biomedical research conducted at universities, academic medical centers, other non-profit organizations, and government laboratories. In the United States, such support comes primarily from the National Institutes of Health (NIH), but also from other federal or state entities, disease focused charities (eg, the Cystic Fibrosis Foundation), or biomedical research philanthropies (eg, the Howard Hughes Medical Institute). Such research often has a key role in elucidating potential drug targets and understanding the pathophysiology of disease—activities that are central to drug discovery. This costly upstream research could stretch back several decades before a drug reaches clinical trials or is approved by the US Food and Drug Administration or another regulator.[1] One recent report found that NIH funding contributed to published research associated with all 210 new drugs approved by the FDA in 2010-16.[2] However, public support often funds later stage translational research as well, and might also cover the conduct of some clinical trials required for drug approval. At some point in the development cycle of most prescription drugs, pharmaceutical manufacturers become involved and often expend substantial resources in moving drugs through pivotal clinical trials and FDA approval and in developing means of large scale production. For some new drugs, their investigation, discovery, and development occur entirely within the corporate sector, but this is uncommon.

The role of public sector contributions versus those of the pharmaceutical industry to drug discovery remains a point of controversy, with some arguing that companies' investment in drug discovery is the key source for new drug development.[3] This view, along with the costs of conducting clinical trials, is used to justify high drug prices,[4-6] although the actual cost of drug development is difficult to accurately estimate.[7] The relative contributions of publicly supported research and the pharmaceutical industry can be difficult to separate for a particular product. However, the upstream, pre-competitive, basic science research that so many new drugs depend on is generally thought to be predominantly funded by public support, while clinical trials are generally thought to be predominantly funded by the pharmaceutical industry.

One way to assess the contributions of various sectors in the drug development continuum is to

define the research that justifies patent claims on the drug—the basis of drug ownership and pricing. Patent-generating research tends to occur later in development because patent law requires inventors to describe a well defined product or process before a patent can be issued. Other patentable steps can cover a drug's synthesis, the chemical composition of its active ingredient, or its method of use. Patents provide the basis for market exclusivity, granting the patent holder ownership over the product and therefore the capacity to control the drug's US price, as well as considerable leverage in pricing negotiations in other healthcare systems. Although patents enable a manufacturer to demand high drug prices, patent based levers have been proposed, and occasionally have been used with success, to achieve public policy goals, such as helping ensure access to essential drugs in low income settings.[8-12]

Previous studies have reviewed the data submitted to the FDA to investigate public sector research support of drug development that is reflected in these patents. Although some follow-on patents are clinically trivial and not germane to a drug's innovative contribution to patient care, the patents submitted to FDA are typically those that are considered key to the drug's invention and clinical use. Earlier analyses found public sector research institutions to be associated with the patents covering 4.6% of new molecular entities approved in 1981-90,[13] 6.7% of new drugs approved in 1990-99,[4] 9.0% of new molecular entities approved in 1988-2005,[14] and, most recently, 13.6% of new molecular entities approved between 1990-2007.[15] This increase in the proportion of publicly supported research contributions has been attributed to the changing nature of drug development, with large manufacturers investing proportionally less in internal basic and translational research themselves.[15]

Biomedical research support from the public sector has continued to grow in recent decades, although until recently it had fallen in inflation adjusted terms. By contrast, more large pharmaceutical manufacturers have focused on purchasing drugs developed in start-up companies, many spun out of public sector research institutions. We therefore sought to examine the extent of publicly supported research for new FDA approved drugs as reflected in patent data from 2008-17, including the role of start-up biotechnology companies emerging from publicly supported research.

Methods

To identify recently approved drugs originating from publicly supported research, we examined patent data listed with the FDA, using an approach similar to that used in previous studies.[4 13-15] The FDA's Orange Book describes the key US patents that have been granted for a drug substance (active ingredient), drug product (formulation and composition), or method of use. The Orange Book does not include other patents that might be held on the drug, such as those on manufacturing processes, although public sector institutions are less likely to contribute to these patents. It also does not include non-US patents or patents that have expired.

The Orange Book could miss patents that expired before drug approval, or intellectual contributions that were never patented, so we used additional data sources to supplement our analysis. The Merck Index, a chemical entity reference, was searched for supplementary patent information. The index generally lists one or two of the most important patents on a given drug, usually on the final formulation of the active ingredient. For many drugs, the Merck Index patent(s) were the same as those found in the Orange Book. Patents that were listed in the Merck Index alone typically had expired before drug approval and therefore were not included in the Orange Book.

The patent data available through these sources does not comprehensively capture all patents on a drug and can underestimate non-patent-based intellectual contributions to new drug discovery, particularly in circumstances where patents were not pursued. Therefore, we also used drug discovery histories to identify key missing intellectual contributions. We used the drug monograph database AdisInsight, as well as our own investigations, as described in detail below.

Data collection

Drug approval

We identified all new drugs approved by the US FDA between 2008 and 2017 using the Drugs@FDA database,[16] including all drugs approved through the new drug application process for small (that is, non-biological) molecular entities. Biological treatments, vaccines, and gene treatments were excluded because they are approved through a separate biological license application pathway for which patent information is not collected by the FDA. Novel drugs were identified based on the FDA's type 1 approval designation (drug products containing a new molecular entity) and FDA lists of new drug approvals by year.[1] Treatment categorisation was assigned on the basis of the drug's initial FDA approved indication.

Approval pathway

We defined a drug's approval pathway using FDA listings of drugs that received standard, priority, accelerated, breakthrough, fast track, first-in-class, or Orphan Drug Act designation; a drug may have received more than one of these definitions. We considered such designations only for a drug's initial approval. In 2008-10, the FDA did not publish fast track designation or classify drugs as first-in-class on their website. For those years, we used other published databases.[17 18] A full list of drugs included in this study and their FDA approval pathways is included in supplementary table S1.

Patents

As described above, we then obtained patent data for each approved drug from several sources. We issued a Freedom of Information Act request to obtain

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historical Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) data files for 2001-17 that, along with a data file from March 2018, were used to obtain patent data submitted to the FDA, including those that might have expired. Since patents can be added after drug approval, we also conducted a manual search of the Orange Book for drugs with no patents listed in data files as of April 2019 and found one additional drug with a patent added by the manufacturer. The FDA requires that certain key patents be submitted by the manufacturer for inclusion in the Orange Book, including patents on the drug's substance (active ingredient), product (formulation and composition), or method of use. The Merck Index was used to supplement patent information and typically listed one or two key patents related to the drug's active ingredient (final formulation) or synthesis.[19]

We next obtained data about the patents granted for the study drugs by using the PatentsView application programing interface developed by the US Patent and Trademark Office and the PatentsView R package, using the programming language R version 3.5.0.[20 21] This process allowed identification of a patent's inventor and the organization that was assigned ownership. Typically, these data reflect the information that was assigned at time of the patent grant. This method would not identify information, such as disclosure of government funding, that was later corrected. We manually investigated patents which could not be queried using this method to determine the inventor and assigned ownership for each product.

Drug monographs

Examining only the patent information from the Orange Book could provide an incomplete definition of the key contributions to a drug's invention if key patents expired before drug approval. We used the Merck Index to identify these patents, although such an approach would miss important contributions in cases in which a patent was intentionally not pursued. Previous studies have used bibliometric approaches to capture public supported research contributions by examining publications or patent citation.[21 4] For example, Cleary et al found every drug approved from 2010-16 had associated NIH funding contributing to published research.[2] But these approaches capture the substantial role of public research on the upstream, basic science research that underpins drug discovery. In this paper, we focus on the later stage contributions by public sector institutions.

We therefore supplemented the patent analyses with the drug monograph database, AdisInsight, which details a drug's discovery history, preclinical and clinical development, regulatory status, and pharmacological properties. To develop the monograph, researchers examine the relevant scientific publications, patents, news media, financial transactions, and regulatory documents to create an expert summary of the drug's development history. AdisInsight then creates a descriptive narrative of the research and development history and assigns classifications of "originators" and "developers" for each drug. The originator usually refers to the institution that AdisInsight reviewers concluded originally invented or discovered the active ingredient, and developers were any institution that helped with conducting, funding, or supporting the clinical trials. Given our interest in the role of late stage research contributions, we focused on the drugs that were listed as originating from publicly supported research institutions.

Because the AdisInsight methodology is proprietary and does not provide explanations for why a monograph classified an institution in a given way, we further studied any drug that listed a publicly supported research institution as an originator in the AdisInsight listing if no Orange Book or Merck Index patent was assigned to that institution. We began with targeted web searches to verify the connection between the drug and the AdisInsight listed originating institution. One author (RKN) searched for evidence of news articles, university press releases, researchers' academic profiles, scientific publications, US Securities and Exchange Commission (SEC) filings, and patents that confirmed that the drug's discovery or development had late stage research contributions from the institution (that is, intellectual contributions similar to a patentable invention, such as the drug's discovery or invention, or method of synthesis). If we found corroborating evidence, we considered the AdisInsight classification to be verified, confirming that the drug was based on publicly supported research contributions, as described further below. In one case, we were unable to corroborate the connection, and did not classify the drug as having a publicly supported research origin.

Drug development histories

Similar to the approach used to verify entries from AdisInsight, we conducted web searches to investigate the development history for each drug in the study. We examined publications focused on drug development (eg, *Nature Reviews Drug Discovery*), researcher or inventor biography pages, news articles, academic technology transfer sites, and Wikipedia entries to identify other late stage research contributions supported by public funds that were not captured in the process above. Because we found evidence for publicly supported research institutions' involvement from our initial web searches, we then conducted targeted searches for the drug and the possible researchers and institutions involved to seek primary academic publications, news media sources, or SEC filings that could verify the public sector institution's role.

Identifying public sector research institutions and spin-off companies

To better understand the development pathway for each drug, we examined the assignee information for each patent (or institution identified from the drug monograph and development history investigations) and conducted web searches to classify the organi-

zation as either a public sector research institution (universities, hospitals, non-profit foundations or institutions, or government laboratories) or a private, non-public organization (primarily biotechnology or pharmaceutical companies). For cases in which a patent had multiple assignees, we characterized the patent as held by a public sector research institution if one or more of the assignees was a public sector institution.

Whenever possible, we identified start-up firms spun out from publicly supported research institutions. For each company, we investigated the foundational history using web searches of the company's website, new articles about the company, Wikipedia entries, SEC filings, and profiles of the company or its founders. Indications that the company was spun out from a publicly supported research institution were followed up to confirm or refute such a connection. For example, we reviewed the company's own description of its founding, university press releases, and university profiles of the academic founder to determine whether the company could fairly be described as an academic spin-off company. Although we identified many companies that were spun out from public sector research institutions, this did not automatically mean the drug in question was based on publicly supported research. To ensure accurate categorization, we investigated whether the FDA approved drug was based on the same technologies or products that had led to the formation of the spin-off company, to characterize whether the drug truly could be considered as being based on an extension of publicly supported research.

Data analysis

Determining public sector contributions

To determine whether a drug had a major research contribution from publicly supported research late in its development, we further analyzed the contributions of the institutions involved in the development. We considered a drug to have been based on public support if we found any patents for the product that were owned by a public sector research institution or that declared government funding for the product (that is, a government interest statement). We also included drugs listed in the drug monograph database as "originating" in a public sector research institution that we could independently verify as well as from our own review of drug development histories as described above. For drugs that were included without patent data, all authors reviewed and agreed with the drug's classification of having late stage, publicly sponsored research contribution. For a combination drug containing a new molecular entity (eg, antiviral treatments), we considered the drug to have contributions from publicly supported research if one or more of the active ingredients had contributions from a publicly supported research, consistent with the approach taken by Stevens et al.[15]

For spin-off companies, as described above, if we found evidence that a drug was based on the same technology or innovation that led to the creation of the company, we classified the drug as having a late stage research contribution from a spin-off company that had its origin in publicly supported research. We excluded drugs that were unrelated to a company's original spin-off product or technology.

Many aspects of a drug can be patented, with some patents representing more important innovation than others. Firstly, for each drug in which one or more patents were central to identifying a publicly sponsored research contribution, we calculated the share of patents held by publicly supported research institutions and their spin-off companies, compared with the total patents identified for that drug. We report below the unweighted average of the share of patents held by publicly supported research institutions and their spin-off companies, with a 95% confidence interval assuming a normal distribution. Secondly, we determined whether the oldest patent identified was held by a publicly supported research institution or a spin-off company. Thirdly, we examined all the Orange Book patents for that drug to determine whether publicly supported research led to patents on its substance (active ingredient) or product (formulation and composition), which are typically more foundational.

To analyze whether drugs based on publicly sponsored research or spin-off contributions were significantly more likely to have been granted expedited FDA review or be a first-in-class drug, we conducted a Fisher's exact test of independence with a Bonferroni adjusted alpha level of 0.007 (0.05/7).

Patient and public involvement

While we recognize that patients and members of the public are the ultimate stakeholders and end users in late stage new drug discovery, we were unable to involve them as partners in considering the research question, the analysis, or the outcomes. The analysis required in-depth legal and specialist knowledge with access to large databases. We plan to make the published information available to key public interest and advocacy groups to further transparency around the pathways to late stage new drug discovery.

Results

Patent and originator information

We identified 248 novel drugs that represented new molecular entities approved for the first time between January 2008 and December 2017 (21 were combinations, of which some had more than one new molecular entity, leading to 253 new molecular entities). Using the FDA Orange Book, we identified at least one patent for 230 (93%) products. The Merck Index identified at least one patent for an additional 14 (6%) products, leaving only five products (2%) with no available patent information. We identified drug monographs for 246 (99%) products, and either patent or monograph data were available for all but one drug (n=247).

Publicly supported research contributions

Our review of patents and supporting data found that a quarter (n=62) of all new products had documented late stage research contributions from a publicly supported research institution or spin-off company. Forty eight products (19% of all new drug approvals) had evidence of direct publicly supported research (table 1 and table 2). For all but one, the contributions were related to the drug's initial discovery, synthesis, or other key intellectual property leading to a patentable invention. For 30 of these drugs, publicly supported research institutions directly held one or more of the key patents. Another seven drugs had direct publicly supported research origins, although the patents listed in the Orange Book were held by a spin-off company. The remainder of drugs with public support contributions was found through the drug monograph database and investigations of the drugs' discovery and development histories. One of these drugs, benznidazole, a treatment for Chagas disease, is a distinct case because it received development support from the Drugs for Neglected Diseases Initiative and others, and is being sold on a "no profit no loss" basis.[22] However, the drug was originally developed by Hoffman-La Roche in the 1970s, which then donated the rights to the drug to the Brazilian government in 2003.[23]

Fourteen (6%) drugs were developed by spin-off companies that were based wholly or in part on publicly supported research; all but two were identified through patents listed in the Orange Book (table 3). For example, the hepatitis C treatment sofosbuvir (Sovaldi) and other sofosbuvir-containing

Table 1 | New drugs with publicly supported research contributions in 2008-12

Approval date (ID)	Drug name (generic)	Manufacturer	Public sector institution	US government contribution*	Source used for origin
20 March 2008 (#022249)	Bendamustine hydrochloride	Cephalon	Institute for Microbiology and Experimental Therapy (former East Germany)	—	Drug history
24 April 2008 (#021964)	Methylnaltrexone bromide	Salix Pharms	University of Chicago (PHS/HHS)	Yes	Patent
3 July 2008 (#022090)	Gadoxetate disodium	Bayer Healthcare	Massachusetts General Hospital	—	AdisInsight
19 September 2008 (#022290)	Iobenguane sulfate 123I	GE Healthcare	University of Michigan	Yes	Patent (Merck Index)
28 October 2008 (#022253)	Lacosamide	UCB	University of Houston/Research Corporation Technologies (NIH)	Yes	Patent, AdisInsight
15 December 2008 (#022311)	Plerixafor	Genzyme	Rega Institute for Medical Research	—	AdisInsight
22 December 2008 (#021711)	Gadofosveset trisodium	Lantheus Medical	Massachusetts General Hospital	—	Patent, AdisInsight
7 April 2009 (#022268)	Artemether, lumefantrine†	Novartis	Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences (China)	Yes	Patent
24 September 2009 (#022468)	Pralatrexate	Allos	Sloan-Kettering Institute for Cancer Research, SRI International, Southern Research Institute (NCI)	Yes	Patent
5 November 2009 (#022393)	Romidepsin	Celgene	Harvard University/University of Tokyo	—	Drug history
16 November 2009 (#022395)	Capsaicin	Acorda	University of California	—	Patent
22 January 2010 (#022250)	Fampridine	Acorda	Purdue University	—	Drug history
13 August 2010 (#022474)	Ulipristal acetate	Lab HRA Pharma	HHS/Research Triangle Institute	Yes	Patent
15 November 2010 (#201532)	Eribulin mesylate	Eisai	Harvard University/NCI	Yes (no patent)	AdisInsight, drug history
28 April 2011 (#202379)	Abiraterone acetate	Janssen Biotech	Institute of Cancer Research (UK)/ University of London	—	Patent, AdisInsight
2 May 2011 (#201280)	Linagliptin	Boehringer Ingelheim	University of Toronto, Tufts College, New England Medical Center Hospitals (NIH)	Yes	Patent
14 October 2011 (#021825)	Deferiprone	Apopharma	Royal Free and University College Medical School/University of Toronto	—	Patent, AdisInsight, drug history
23 January 2012 (#202833)	Ingenol mebutate	Leo Labs	NCI (US)/University of Queensland (Australia)	Yes (no patent)	Patent, AdisInsight, drug history
31 January 2012 (#203188)	Ivacaftor	Vertex Pharms	Cystic Fibrosis Foundation Therapeutics	—	AdisInsight
6 March 2012 (#021746)	Lucinactant	Windtree Therapeutics	Scripps Research Institute	—	Patent
6 April 2012 (#202008)	Florbetapir 18F	Avid Radiopharms	University of Pennsylvania (NIH)	Yes	Patent
27 August 2012 (#203100)	Cobicistat, elvitegravir, emtricitabine‡, tenofovir disoproxil fumarate	Gilead Sciences	Emory University (NIH)	Yes	Patent
31 August 2012 (#203415)	Enzalutamide	Astellas	University of California (US Army, NIH)	Yes	Patent
12 September 2012 (#203155)	Choline 11C	MCPRF	Mayo Clinic	—	Drug history
21 December 2012 (#203441)	Teduglutide recombinant	NPS Pharms	Toronto General Hospital, University of Toronto	—	Patent, AdisInsight
21 December 2012 (#203858)	Lomitapide mesylate	Aegerion	University of Pennsylvania	—	Patent

NIH=National Institutes of Health; NCI=National Cancer Institute; PHS=US Public Health Service; HHS=US Department of Health and Human Services.
*Considered to have US government contributions if the drug originated at a US government lab, a patent was assigned to a US government agency, or a patent declared US government funding of the invention. Two drugs had origins with the National Cancer Institute, although no patents were found to be held by the NCI.
†Artemether and lumefantrine are both new molecular entities with publicly supported origins, but are counted as one product in this analysis.
‡This combination product contains the new molecular entity elvitegravir, but it is included as having a publicly supported origin because emtricitabine originated at Emory. This product represented the first time elvitegravir was approved by the US Food and Drug Administration.

combination drugs were in this category because they originated at Pharmasset, a spin-off company based on federally funded research performed at Emory University.[24] In addition to these 14 drugs, at least 10 other drugs had origins in spin-off companies, but these were excluded because it was unclear whether these drugs were related to the technologies or drugs that initially gave rise to the spin-off company. Full details of the rationale used to classify drugs as having publicly supported or spin-off research contributions can be found in appendix 1.

We identified most of the drugs that had publicly sponsored research or spin-off contributions through patent data available through the Orange Book (n=47). Two were found from patents in the Merck Index, while eight came from the drug monograph classification and five from our own drug history investigations. The contributions of each of the date sources are shown in figure 1. The data sources had strong concordance (appendix 2).

Contributions by drug class

Late stage, publicly supported research contributions by drug class were concordant with the overall total number of approvals by drug class (table S2). In hematology-oncology, 17 (27%) drugs were based on publicly supported research; 13 (33%) drugs were in infectious diseases, and 10 (63%) were among diagnostics agents Each of these drug classes had a higher share of drugs from publicly supported research than the average in our sample. Conversely, for psychiatric drugs, we did not find late stage, publicly supported research contributions for any of the 15 recently approved drugs.

Patent characteristics

Of the 48 drugs identified as having late stage, publicly supported research contributions, 38 (80%) had at least one patent held by a publicly supported research institution or spin-off company. For these drugs, 70% (95% confidence interval 60% to 81%) of the patents, on average, were held by a publicly supported research institution or spin-off (table 4). A US government interest statement was declared on at least one patent in the case of 17 drugs. For 32 (84%) drugs, the oldest patent identified was held by a publicly supported research institution or spin-off company. Of the 35 drugs for which we identified at least one Orange

Table 2 | New drugs with publicly supported research contributions in 2013-17

Approval date (ID)	Drug name (generic)	Manufacturer	Public sector institution	US government contribution*	Source used for origin
25 January 2013 (#022271)	Alogliptin benzoate	Takeda Pharms USA	University of Toronto, Tufts College, New England Medical Center Hospitals (NIH)	Yes	Patent
13 March 2013 (#202207)	Technetium 99mTc tilmanocept	Cardinal Health 414	University of California-San Diego (NIH)	Yes	Patent
25 October 2013 (#203137)	Flutemetamol 18F	GE Healthcare	University of Pittsburgh	—	Patent
19 March 2014 (#204684)	Miltefosine	Knight Therapeutics	Max Planck Institute (Germany)	—	Patent (Merck index)
19 March 2014 (#204677)	Florbetaben 18F	Piramal Imaging	University of Pennsylvania (NIH)	Yes	Patent
19 August 2014 (#205494)	Eliglustat tartrate	Genzyme	University of Michigan (NIH)	Yes	Patent
19 December 2014 (#206162)	Olaparib	Astrazeneca Pharms	University of Sheffield/Yorkshire Cancer Research/ Institute of Cancer Research/University of Cambridge (UK)	—	Patent, AdisInsight
19 December 2014 (#206426)	Peramivir	Biocryst	University of Alabama-Birmingham	—	Patent, AdisInsight
29 April 2015 (#206333)	Deoxycholic acid	Kythera Biopharms	University of California-Los Angeles	—	Patent
2 July 2015 (#206038)	Ivacaftor, lumacaftor	Vertex Pharms	Cystic Fibrosis Foundation Therapeutics	—	AdisInsight
23 October 2015 (#207953)	Trabectedin	Janssen Prods	University of Illinois	—	AdisInsight
5 November 2015 (#207561)	Cobicistat, elvitegravir, emtricitabine†, tenofovir alafenamide fumarate	Gilead Sciences	Emory (NIH)	Yes	Patent
11 April 2016 (#208573)	Venetoclax	Abbvie	Walter and Eliza Hall Institute of Medical Research	—	Patent
27 May 2016 (#208054)	Fluciclovine 18F	Blue Earth	Emory University (Department of Energy)	Yes	Patent
29 May 2016 (#207999)	Obeticholic acid	Intercept Pharms	University of Perugia (Italy)	—	Patent, AdisInsight
19 September 2016 (#206488)	Eteplirsen	Sarepta Therapeutics	Leiden University Medical Center (Netherlands)/University of Western Australia	—	Patent
19 December 2016 (#209115)	Rucaparib camsylate	Clovis Oncology	Newcastle University (UK)/Cancer Research UK	—	Patent
23 December 2016 (#209531)	Nusinersen sodium	Biogen Idec	University of Massachusetts (NIH)/ Cold Spring Harbor Laboratory	Yes	Patent
29 April 2017 (#207997)	Midostaurin	Novartis Pharms	Dana Farber Cancer Institute	—	Patent
29 August 2017 (#209570)	Benznidazole‡	Chemo Research SL	Brazilian government, Drugs for Neglected Diseases Initiative Foundation	—	Drug history
18 December 2017 (#208254)	Netarsudil dimesylate	Aerie Pharms	Duke University	—	Patent, AdisInsight
21 December 2017 (#209360)	Angiotensin II acetate	La Jolla Pharm	George Washington University	—	Patent

NIH=National Institutes of Health.
*Considered to have US government contributions if the drug originated at a US government lab, a patent was assigned to a US government agency, or a patent declared US government funding of the invention. Two drugs had origins with the National Cancer Institute, although no patents were found to be held by the NCI.
†This combination product contains the new molecular entity tenofovir alafenamide fumarate, but it is included as having a publicly supported origin because emtricitabine originated at Emory. This product represented the first time tenofovir alafenamide fumarate was approved by the US Food and Drug Administration.
‡Benzinidazole represents a distinct case; it was discovered through research at Hoffman-LaRoche and not through publicly supported research. However, Hoffman-LaRoche donated the rights to the drug to the Brazilian government. In addition, the Drug for Neglected Diseases Initiative Foundation supported the development and Food and Drug Administration approval of the drug in the US and is being sold on a "no profit no loss" bas[15].22

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Table 3 | New drugs with contributions from spin-off companies based on publicly supported research

Approval date (ID)	Drug name (generic)	Manufacturer	Spin-off company	Public sector institution	Source
1/18/2008 (#022187)	Etravirine*	Janssen R and D	Tibotec	Rega Institute	Patent, AdisInsight
1/14/2011 (#022454)	Ioflupane 123I	GE Healthcare	Research Biochemicals International	Northeastern University	Patent
5/20/2011 (#202022)	Rilpivirine hydrochloride*	Janssen Prods	Tibotec	Rega Institute	Patent, AdisInsight
8/17/2011 (#202429)	Vemurafenib	Hoffmann-La Roche	Plexxikon	Yale University/University of California-Berkeley	Patent
7/20/2012 (#202714)	Carfilzomib	Onyx Therapeutics	Proteolix	Yale University/California Institute of Technology	Patent
8/30/2012 (#202811)	Linaclotide	Allergan Sales	Microbia	Whitehead Institute	Patent
5/15/2013 (#203971)	Radium 223Ra dichloride	Bayer Healthcare	Anticancer Therapeutic Inventions	Norwegian Radium Hospital, University of Oslo	Patent
12/6/2013 (#204671)	Sofosbuvir	Gilead Sciences	Pharmasset	Emory University	Patent
7/7/2014 (#204427)	Tavaborole	Anacor Pharms	Anacor Pharmaceuticals	Stanford University/ Pennsylvania State University	Patent
10/10/2014 (#205834)	Ledipasvir†, sofosbuvir	Gilead Sciences	Pharmasset	Emory University	Patent
6/28/2016 (#208341)	Sofosbuvir, velpatasvir†	Gilead Sciences	Pharmasset	Emory University	Patent
3/13/2017 (#209092)	Ribociclib succinate	Novartis Pharms	Astex Therapeutics	University of Cambridge	Patent
6/19/2017 (#208610)	Delafloxacin meglumine	Melinta	Melinta	Yale University	Patent
7/18/2017 (#209195)	Sofosbuvir, velpatasvir, voxilaprevir†	Gilead Sciences	Pharmasset	Emory University	Patent

*Both etravirine and rilpivirine are non-nucleoside reverse transcriptase inhibitors and are successors to the TIBO compound discovered at the Rega Institute. This discovery led to the spin-off company Tibotec (later bought by Johnson and Johnson and merged with its Janssen division). The Orange Book patents were held by Janssen.
†Ledipasvir, velpatasvir, and voxilaprevir are all new molecular entities approved as combination products with a sofosbuvir backbone. Sofosbuvir originated at the spin-off company Pharmasset, and therefore each of these combination products are considered to have a spin-off origin.

Book patent held by a publicly supported research institution or spin-off company, 27 (77%) had at least one patent held on the key properties of the drug's product or substance. Similar findings applied to drugs with late stage contributions from a spin-off company (table 4).

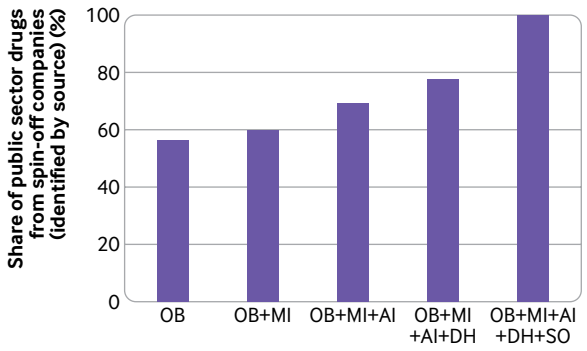

Fig 1 | Proportion of new drugs with publicly sponsored research or from spin-off companies, identified by data source. The figure shows the breakdown of the relative share of the data sources used to identify publicly supported research contributions. The first four columns represent the drugs identified as having public sponsored research origins, and the last column represents those with spin-off company origins. Most drugs identified as publicly supported research contributions had Orange Book patents assigned to either to a public sector institution (28/62) or spin-off company (an additional 7/62). Two more drugs were primarily identified by Merck Index patents, six by AdisInsight entries, and five by the authors' investigation of the drug's history. Finally, 14 drugs were identified as originating in a spin-off company. For the spin-off drugs, 12 had Orange Book patents held by the spin-off company (the remaining two had Orange Book patents held by the successor company of the spin-off). OB=Orange book; MI=Merck Index; AI=AdisInsight; DH=drug history (author's investigation); SO=spin-off company

FDA approval process

New drugs based on contributions from publicly supported research or spin-off companies were substantially more likely to receive FDA approval through one or more expedited development or review pathways than new drugs without these characteristics (68% *v* 47%, P=0.005) and to be first in class (45% *v* 26%, P=0.007; table 5). Both are indicators of potentially greater therapeutic importance.

Discussion

Principal findings

In the present study, we studied all new drugs approved by the FDA in 2008-17 to determine whether their patents or other late stage, drug discovery contributions documented origins in publicly supported research. The development of a new drug treatment is a complicated process. Important and costly contributions come from both the public and the private sectors, in varying proportions. Under current patent law, making a seminal discovery about an important drug target, or even taking development of a new approach almost to the point of creating a marketable product, are not sufficient to win intellectual property rights to the drug that emerges from this chain of research. However, an entity (usually

Table 4 | Characteristics of patents on new drugs with origins in publicly supported research contributions. Data are number of drugs unless stated otherwise

Patent characteristic	No of drugs by patent characteristics		
	Publicly sponsored research contribution (n=48)	Spin-off company based on publicly sponsored research (n=14)	Total (n=62)
None identified from public sector institution or spin-off companies	10	2*	12
≥1 identified from public sector institution or spin-off company†	38	12	50
≥1 held by public sector institution‡	30	0	30
≥1 held by public sector institution's spin-off company	14	12	26
≥1 declares government funding	17	0	17
Share of patents held by public sector institution or spin-off company (95% CI; N=38, N=12)	0.70 (0.60 to 0.81)	0.81 (0.64 to 0.98)	0.72 (0.63 to 0.81)
Public sector institution or spin-off company holds first patent	32	12	44
Drugs with ≥1 patent held by public sector institution that is listed in Orange Book	28	0	28
Drugs with ≥1 patent held by public sector institution or spin-off company that is listed in Orange Book	35	12	47
Drugs with ≥1 patent held by public sector institution or spin-off company on drug substance	25§	10	35
Drugs with ≥1 patent held by public sector institution or spin-off company on drug product	21¶	9	30
Drugs with ≥1 patent held by public sector institution or spin-off company on drug product or substance	27**	11	38

*Patents held by a successor company of the spin-off company, but not the original spin-off company itself.
†Patents identified predominantly from the Orange Book (n=35), with additional patents identified by the Merck Index (n=2) and AdisInsight listing (n=1).
‡Patents identified predominantly from the Orange Book (n=28), with additional patents identified by the Merck Index (n=2).
§Seven drugs had no patents on drug substance.
¶Six drugs had no patents on drug product.
**Three drugs had no patents on either drug substance or drug product.

a pharmaceutical company) that performs these final steps is usually granted ownership over the product, and thus the chance to establish its price (in the US) and own the revenue it generates. Substantial private investment from industry is critical for many drugs for basic and clinical research, but by funding the clinical trials and the regulatory compliance necessary to win FDA approval, the role of the publicly supported research investments that served as the basis of the drug's discovery are often not as clearly attributed.

Our analysis found that publicly supported research in non-profit institutions (19%) or spin-off companies that had their origins in public funded research (6%) made important late stage intellectual contributions to at least one in four new drugs approved in the past decade. These data highlight the substantial and increasing role of late stage, publicly supported research in the development of new drugs (fig 2),[4 13-15] in addition to the more widely acknowledged contributions of public funding to the foundational basic science discoveries on which most new products are based.

Strengths and limitations of study

This study had several limitations. Firstly, we identified a product as having a late stage, publicly supported research component if the patent and drug discovery history documented a key contribution by a public sector entity or spin-off company in its development. This method does not confirm that such public investment was the only source of a drug's creation, or that there was no private sector contribution. We did not attempt to weigh the relative importance of public versus private sector innovation for particular drugs; for many products, important corporate investment occurred as well. As a result, the substantial contributions of public support to late stage drug development would not confer partial public ownership of most of these products under current patent law. In fact, this flow of publicly funded research knowledge into the private sector for commercialization seems to have been a major goal of the original Bayh-Dole legislation, rather than an unintended consequence of it.[25]

Secondly, our analysis relies primarily on patents listed in the Orange Book and proprietary databases of drug development to identify public sector origins, which represents a limited set of patents associated with a drug, even though these patents are generally considered the most important in a product's intellectual genealogy. Further investigation into the origins of each drug might have yielded additional relevant information. This approach might underestimate the contributions of publicly supported and academically based researchers who collaborate with pharmaceutical companies if a patent derived from such collaboration is held by the sponsor. For example, Ciba-Geigy (now Novartis) held the patent for imatinib for years but had not developed the product clinically until Brian Drucker at Oregon Health and Science University persuaded the company to provide him with samples of it for his research on chronic myeloid leukemia, leading to the profitable product Gleevec, approved in 2001.[26] Although that drug preceded the study period under consideration, the

Table 5 | Regulatory designations and other classifications of new drugs by the US Food and Drug Administration. Data are number (%) of drugs unless stated otherwise

FDA designation or classification of drug	Drug origin			P value†
	Publicly supported (n=48)	Publicly supported or from spin-off company (n=62)	Not publicly supported in origin (n=186)	
Priority review	26 (57)	36 (58)	78 (42)	0.04
Breakthrough therapy*	4 (8)	8 (13)	18 (10)	0.48
Accelerated approval	8 (17)	10 (16)	19 (10)	0.25
Fast track	14 (29)	22 (35)	52 (28)	0.27
≥1 expedited designation	31 (65)	42 (68)	87 (47)	0.005
First in class	22 (46)	28 (45)	48 (26)	0.007
Rare disease treatment	24 (50)	26 (42)	56 (30)	0.09

*The breakthrough therapy designation was established in 2012 by the FDA Safety and Innovation Act. The first new molecular entity received this designation in November 2013.
†Fisher's exact test of independence was conducted to test drugs from public sector institutions or spin-off companies against those drugs not publicly supported.

patents on the drugs were held by Novartis and there was no patent evidence held by (or royalty payments made to) the academic medical center that was essential in its development.

A third limitation is that we did not include biological agents in this study despite their clinical and economic importance. This exclusion was because the FDA does not collect patent data for drugs approved through the Biologic License Application process. Biological medicines represent an increasingly important component of drug treatment both clinically and economically, and the current regulatory framework limits the opportunity to produce generic drugs. Further research to investigate the role of late stage publicly supported research for biological medicines is necessary. Lastly, we limited our investigations to English language publications, websites, and media coverage to verify key contributions made by publicly supported research.

Our approach is not the only way of quantifying public sector research contributions, because it could miss a great deal of important scientific discovery funded and conducted with the support of public funding. The patent based approach used also underestimated the additional role of upstream basic and translational science research supported by public funds that is critical to the discovery of new drugs; this contribution has been clearly described by others.[2 27] In addition, previous studies in the US and the UK have shown how publicly funded research create substantial direct and indirect economic value, complementing private industry research expenditure, innovation, and privately held patents.[28 29] Thus, our approach does not capture the totality of returns generated as a result of public investment.[30]

Our analysis did not consider the relative amounts of financing that comes from public and private sector sources. We did not tabulate the cost of clinical development within industry required for final product development and regulatory approval, which can be substantial. We also did not consider the substantial public subsidies for the drug development enterprise, which include federal expenditures in the form of research and development tax credits and the Orphan

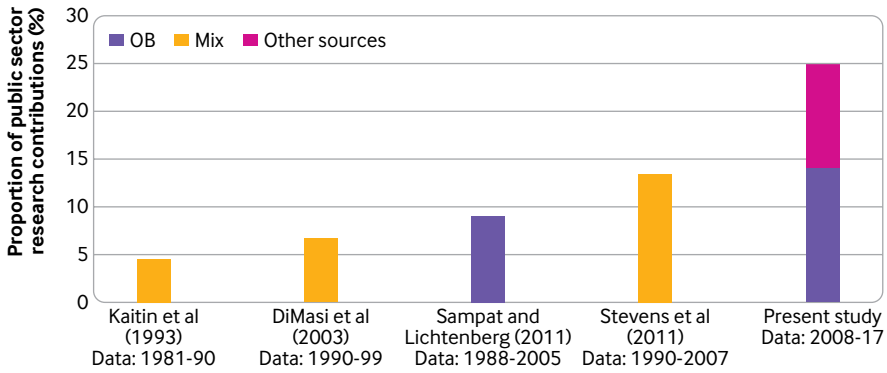

Fig 2 | Changes in rates of publicly sponsored research contributions to new drug discovery, by study over time with data sources used. The figure compares the present study with previous studies examining public sector contributions to new drug discovery via patent analysis. The Kaitin and DiMasi studies used the Tufts Center for the Study of Drug Development databases that use Orange Book patents as well as other proprietary datasets (not fully described). The analysis by Sampat and Lichtenberg examined patents listed only in the Orange Book. The Stevens et al study examined the Orange Book, proprietary licensing databases, and conducted a survey of university technology transfer managers to identify drugs that originated in public sector institutions. The relative contributions of the various sources were not disclosed, and how the studies dealt with contributions from public sector spin-off companies is not clear. However, the study period for Stevens et al was similar to that of Sampat and Lichtenberg, so the difference between their findings might be a result of the additional sources used. OB=Orange Book

Drug Act tax credit, which was a subsidy equal to 50% of the cost of the qualifying trial (until 2017, when it was reduced to 25%). Our study also did not take into account direct funding of drug development in the form of publicly funded clinical trials as well as research and small business grants, and indirect support in the form of public sector research institutions hosting industry funded clinical trials.

Comparison with other studies

One difference between our analysis and previous studies is that earlier research relied predominantly on patent data provided in the FDA Orange Book,[4 13-15] which could underestimate the role of publicly supported research if patents had expired at the time of drug approval, were never pursued, or were held by spin-off companies. Limiting our analysis to only those drugs with Orange Book patents held by public sector research institutions would have identified 28 drugs, or just 11% of new approvals (table 4). We would have missed, for example, an additional seven drugs that were ultimately determined to have publicly supported research origins, but the listed Orange Book patents were held by spin-off companies. Incorporating other patent sources, drug histories, and basic investigations to confirm a drug's development history, including the role of spin-off companies with origins in publicly support research, more accurately represents the late stage contributions of public sector funding to drug discovery and development.

These findings also reflect the continuing trend of an increasing role of publicly supported research in late stage research leading to new drug discovery, which has also been seen in previous studies (fig 2).[4 13-15] This increasing trend might be because of ongoing congressional funding of biomedical research through the NIH since the 1990s.[31 32] The fruits of that earlier publicly supported research would be seen in recent drug approvals, because it typically takes a decade or more from drug discovery to approval. In addition, university-owned patents of all kinds have increased as a share of all US patents from 0.28% in 1969 to 0.83% in 1985 to 1.89% in 2012.[33] This rising share reflects increased productivity as a result of more biomedical research funding as well as policies to more actively pursue patents by academic technology transfer offices in the nearly four decades since passage of the Bayh-Dole Act.[34] For example, we identified at least 17 drugs for which US government interest was disclosed on patents; this number is likely to be an underestimate owing to evidence that government funding is underdisclosed on patent applications.[9 35 36] Because our study examined the assignee data on the patent grants, we would miss any updates submitted to the US Patent and Trademark Office of corrections clarifying government contributions. Recent analysis found these corrective updates to be as high as 20-30% of all patents for some academic insitutions.[37]

Our data also indicate that drugs with contributions from publicly supported research or spin-off companies are 1.4 times as likely to receive an expedited FDA approval process and 1.7 times as likely to be first in class (table 5). Although these data are crude measures of innovativeness, they suggest that publicly supported research is not only leading to new drugs but also leading to new classes of drugs with novel mechanisms of action, a finding consistent with previous studies.[15 29 38-40]

Policy implications

These findings have several implications for healthcare and regulatory policy, particularly in the US. The US biomedical enterprise underlies a substantial proportion of new drug development,[41] although by no means all of it.[42] At the same time, drug prices are substantially higher in the US than anywhere else in the world, with Americans paying on average about twice the per capita amount for prescription drugs as citizens of other advanced industrialized contries.[43 44] Identification of drugs with late stage, publicly supported research contributions, particularly those for which such institutions hold key patents, could represent a useful policy lever. Such drugs include nusinersen (Spinraza, for spinal muscular atrophy; list price US$750 000 (£610 400; €685 000) in the first year of use),[45] eliglustat (Cerdelga, for Gaucher disease; $310 250/year),[46] and enzalutamide (Xtandi, for prostate cancer; $129 000/year).[47] The prices of these drugs, each of which relied on substantial academic development, have been criticized in the US and all are substantially lower in other countries.

For these and other drugs, the contributions of publicly funded research to their development could be expected to be compensated by more favorable pricing to payors, the largest of which is the US government itself. Although the university that largely developed Xtandi did receive a lucrative licensing agreement, such compensation is often not the case. Whether such payments—most of them far less lucrative—represent adequate compensation to the innovator institution for its role in drug development is unclear.[48] In addition, such agreements when they exist do not benefit those who purchase these drugs at such high prices. Beside commercial insurers and state governments, such payors include the federal government and patients themselves—all of whom have already made investments into a drug's creation, such as through taxpayer support of NIH funding.[49 50] Given the current US debate on whether the public is getting a fair return on public investment[51] and when rising drug prices are defended as being necessary to fund industry innovation, without which new treatments would be expected to slow dramatically, our findings can inform this public discussion.

In theory, the US government retains a fully paid license, as well as so-called march-in rights, for patents with government funded origins. These provisions could allow the government to use the patented product for its own purposes or, in the case of march-in rights, grant additional licenses to others if needed to address health needs. Raising the prospect of using these authorities has had some effect in cases in which the NIH helped negotiate agreements

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on the licensing of stem cell patents. In addition, the US Centers for Disease Control and Prevention was able to liberalize the licensing of patents related to avian flu, and the manufacturer of ritonavir reduced a planned price increase for government agencies after a march-in petition was submitted to the NIH.[52] But to our knowledge, neither authority has ever been activated by a federal agency for any drug, even in the face of critical drug shortages or extreme price spikes.[8] Of course, these legal authorities, even if they were ever to be exercised, would only apply to drugs for which government patent rights can be identified. Government interest statements are underdisclosed and this study represents only a limited patent landscape analysis for each drug; thus, only a subset of drugs with public sector contributions in this study had definitively identified US government interests.

However, hundreds of public sector institutions have recognized their ethical obligation to make technology transfer agreements that will promote the public's interest and equitable access to medicines, although how well these principles are practiced by many institutions is unclear.[10-12] While these technology transfer principles were developed and implemented primarily to promote access in low and middle income countries, this approach could also be used to ensure the public has access to very costly taxpayer funded drugs. Additionally, other broadly applicable policy tools might be available, such as negotiating lower drug prices (currently not in practice in the US) or even issuing compulsory licenses to meet public health needs regardless of drug origin or patent ownership, although greater justifications for the use of such interventions might be needed for high priced drugs with identified public sector contributions.

Conclusion

We reviewed comprehensive patent and related data to trace the intellectual contributions of publicly supported research to the discovery and development of new drugs. Our findings highlight the important role of public and philanthropic funding in the drug research and development ecosystem. We found that such institutions and their corporate spin-off companies were central to the development of at least a quarter of all new drugs approved by the FDA in 2008-17, either through direct contributions to drug development or through the formation of spin-off companies based on earlier public funding. Drugs approved following major public sector funding were more likely to receive an expedited development or approval pathway designation from the FDA and more likely to be a first-in-class treatment, suggesting that they were more likely to be novel and potentially clinically important.

Our findings also document a substantial increase in the share of drugs in the US with publicly supported research origins compared with previous studies. This increased share could reflect our more comprehensive methodological approach as well as growing taxpayer funding for biomedical research and increased pursuit of patents by public supported research institutions over the past few decades. These findings provide additional data for the ongoing debate on support for public sector biomedical research, and the best ways to take these key contributions into account in determining the ownership of and fair prices for new drugs, especially those priced at very high levels.

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Ethical approval: This study was not submitted for institutional review board review because it is based on publicly available data and involved no health records (45 Code of Federal Regulations [CFR] 46.102).

Data sharing: No additional data available.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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50 Pear R. 'Paying twice': a push for affordable prices for taxpayer-funded drugs. New York Times. 2018 https://www.nytimes.com/2018/05/28/us/politics/drug-prices.html
51 Mazzucato M, Roy V. Rethinking value in health innovation: from mystifications towards prescriptions. November, 2017. https://www.ucl.ac.uk/bartlett/public-purpose/publications/2018/jan/rethinking-value-health-innovation-mystifications-towards-prescriptions
52 KEI Comments Regarding the NIST Special Publication 1234 Draft Green Paper on Return on Public Investment. January, 2018. https://www.keionline.org/wp-content/uploads/2019/01/KEI-comments-NIST-SP-1234-ROI-9Jan2018.pdf

Web appendix 1: Detailed explanation for including drugs with publicly supported and spinoff contributions
Web appendix 2: Data sources
Web appendix 3: Supplementary tables

Appendix 1: Detailed explanation for including drugs with publicly-supported and spinoff contributions

Table 1: New drugs with publicly-supported research contributions

Drug Name (Generic)	Public Sector Institution	Source Used for Origin	Rationale for Inclusion
BENDAMUSTINE HYDROCHLORIDE	Institute for Microbiology and Experimental Therapy (German Democratic Republic)	Drug History	Bendamustine was first synthesized in 1963 by Ozegowski and Krebs (Institute for Microbiology and Experimental Therapy) in East Germany (the former German Democratic Republic). Until 1990, it was available only in East Germany.[1]
METHYLNALTREXONE BROMIDE	University of Chicago (PHS/HHS)	Patent	Orange Book patents: US 6559158 assigned to University of Chicago. The US government retains rights on this patent (M01 RR00055 awarded by the U.S. Public Health Service General Clinical Research Center).
GADOXETATE DISODIUM	Massachusetts General Hospital	AdisInsight	Gadoxetate disodium is a hydrophilic paramagnetic contrast agent developed by Schering AG for hepatobiliary MRI. Schering AG acquired a license to EPIX Medical's patents covering liver-enhancing agents such as gadoxetate disodium injection. These included US patents (4899755 and 4888008) that EPIX Medical licensed from the

[1]Tageja N. Bendamustine: safety and efficacy in the management of indolent non-hodgkins lymphoma. Clin Med Insights Oncol. 2011;5:145–156. doi:10.4137/CMO.S6085

			Massachusetts General Hospital (MGH). The MGH patents covered albumin-targeted agents such as MS 325 (AngioMARK).[2]
IOBENGUANE SULFATE I-123	University of Michigan	Patent (Merck Index)	Merck Index patent: US 4584187 held by the University of Michigan. The US government retains rights on this patent (U.S. Department of Energy Contract No. DE-AC02-76EV02031).
LACOSAMIDE	University of Houston / Research Corporation Technologies (NIH)	Patent, AdisInsight	Orange Book patents: US 5654301 and RE38551 that are assigned by Research Corporation Technologies, Inc. and held by Dr. Harold Kohn of the University of Houston. Lacosamide was discovered in 1996 by Kohn and colleagues at the University of Houston.[3] The US government retains rights on this patent (NIH funding, no grant number specified).
PLERIXAFOR	Rega Institute for Medical Research	AdisInsight	Erik De Clercq at the Rega Institute for Medical Research collaborated with Johnson Matthey to synthesize AMD3100, which was mainly discovered as an anti-HIV agent. The molecule (Plerixafor, MozibilTM) was then repurposed for the mobilization of hematopoietic stem cells.[4,5]

[2] Gadoxate disodium: gadolinium EOB DTPA, gadoxetic acid, Gd-EOB-DTPA. Drugs R D. 2004;5(4):227-230. doi:10.2165/00126839-200405040-00008
[3] Choi D, Stables JP, Kohn H. Synthesis and anticonvulsant activities of N-Benzyl-2-acetamidopropionamide derivatives. J Med Chem. 1996;39(9):1907-1916. doi:10.1021/jm9508705
[4] De Clercq E. The bicyclam AMD3100 story. Nat Rev Drug Discov. 2003;2(7):581-587. doi:10.1038/nrd1134
[5] Plerixafor: AMD 3100, AMD3100, JM 3100, SDZ SID 791. Drugs R D. 2007;8(2):113-119. doi:10.2165/00126839-200708020-00006

GADOFOSVESET TRISODIUM	Massachusetts General Hospital	Patent, AdisInsight	Orange Book patents: US 6676929, held by Dr. Lauffer and colleagues and assigned to Lantheus Medical Imaging. Originally developed at the Massachusetts General Hospital NMR Center by Dr. Lauffer.[6]
ARTEMETHER; LUMEFANTRINE**	Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences (China)	Patent	Orange Book patents: US 5677331 assigned to Institute of Microbiology and Epidemiology / Academy of Military Medical Sciences (China).
PRALATREXATE	Sloan-Kettering Institute for Cancer Research, SRI International, Southern Research Institute (NCI)	Patent	Orange Book patents: US 6028071, 7622470, 8299078 The US government retains rights on at least US 7622470 (NIH grants CA092074 and CA 0172(00))
ROMIDEPSIN	Harvard University/University of Tokyo	Drug History	The first total synthesis of romidepsin was accomplished by Harvard researchers and published in 1996. Its mechanism of action was elucidated in 1998 by a joint collaboration between researchers from Fujisawa and University of Tokyo.[7,8]

[6] MGH Department of Radiology. Magnetic Resonance Angiography Using a Blood-Pool Contrast Agent, Gadofosveset. https://www.massgeneral.org/imaging/news/radrounds/june_2012/. Published 2012. Accessed August 8, 2019

[7] Li KW, Wu J, Xing W, Simon JA. Total Synthesis of the Antitumor Depsipeptide FR-901,228. J Am Chem Soc. 1996;118(30):7237-7238. doi:10.1021/ja9613724

[8] Nakajima H, Kim YB, Terano H, Yoshida M, Horinouchi S. FR901228, a potent antitumor antibiotic, is a novel histone deacetylase inhibitor. Exp Cell Res. 1998;241(1):126-133. doi:10.1006/excr.1998.4027

CAPSAICIN	University of California	Patent	Orange Book patents: US 6239180 assigned to The Regents of the University of California.
DALFAMPRIDINE	Purdue University	Drug History	Purdue University holds the patent on the use of pyridines to treat injured mammalian nerve tissue. Richard Borgens, Riyi Shi, both Purdue University researchers, are named inventors on the patent US 8729107B2 (NIH grant NS050174 declared and the US government retains rights to the patent).[99] Purdue University claims the drug as part of its technology transfer portfolio and former Purdue professor Andrew Blight went on to be the Chief Scientific Officer of Acorda Therapeutic that developed the drug.[10]
ULIPRISTAL ACETATE	US Department of Health and Human Services / Research Triangle Institute	Patent	Orange Book patents: US 9283233 assigned to US Department of Health and Human Services. The invention occurred during a joint research agreement between various US government funding agencies and Laboratoire HRA Pharma. Merck Index patent: US 4954490 assigned to the Research Triangle Institute.
ERIBULIN MESYLATE	Harvard University/ National Cancer Institute	AdisInsight, Drug History	Yoshito Kish of Harvard University developed a completely synthetic halichondrin B and found that its cytotoxicity was a function of

[9] Purdue College of Veterinary Medicine. Possible New Treatment for Spinal Cord Injuries Identified in Research Led by PVM Professor. https://www.purdue.edu/vet/news/possible-new-treatment-for-spinal-cord-injuries-identified-in-research-led-by-pvm-professor.php. Accessed August 8, 2019.
[10] Purdue University: Purdue Institute for Drug Discovery. Ampyra. Accessed at: https://www.purdue.edu/discoverypark/drug-discovery/clinical-translation/entities/ampyra.php. Accessed August 8, 2019.

			macrocyclic lactone C1-C38 moiety. This synthetic technology was licensed from Harvard to Eisai, which completed the synthesis of Eribulin mesylate.[11] The National Cancer Institute also directly contributed to the discovery and commercialization, including identifying mechanism of action, screening for anticancer activities, pre-clinical development studies, and first-in-human Phase I clinical trials under a CRADA with Eisai.[12]
ABIRATERONE ACETATE	The Institute of Cancer Research (UK)/ University of London	Patent, AdisInsight	Orange Book patents: US 5604213 assigned to British Technology Group, a British technology transfer organizing that was founded to commercialize publicly-funded research. Abiraterone was discovered and developed by Mike Jarman, Elaine Barrie, and Gerry Potter at the Cancer Research UK (CRUK) Centre for Cancer Therapeutics in the Institute of Cancer Research, London (GB9207057.2 also assigned to British Technology Group).[13]
LINAGLIPTIN	University of Toronto, Tufts College, New England	Patent	Orange Book patents: US6890898, 7078381, 7459428 assigned variously to the Trustees of Tufts College, New England Medical

[11] Swami U, Chaudhary I, Ghalib MH, Goel S. Eribulin -- a review of preclinical and clinical studies. Crit Rev Oncol Hematol. 2012;81(2):163-184. doi:10.1016/j.critrevonc.2011.03.002

[12] NCI Technology Transfer Center. Halaven® - eribulin mesylate (analog of halichondrin B). https://techtransfer.cancer.gov/aboutttc/successstories/eribulin-mesylate. Published 2016. Accessed August 8, 2019.

[13]The Institute of Cancer Research. Abiraterone: a story of scientific innovation and commercial partnership. https://www.icr.ac.uk/news-features/latest-features/abiraterone-a-story-of-scientific-innovation-and-commercial-partnership. Published 2014. Accessed August 8, 2019.

	Medical Center Hospitals (NIH)		Center Hospitals, and 1149336 Ontario Inc (a spin-off of University of Toronto led by Daniel Drucker). These patents are on methods of regulating glucose related to DPP-4. The US government retains rights on each of those patents (NIH funding).
DEFERIPRONE	Royal Free and University College Medical School / University of Toronto	Patent, AdisInsight, Drug History	Deferipone was identified by George Kontoghiorghes and colleagues at University College Hospital (UK) and later at Royal Free Medical School, with work funded by UK Thalassemia Society (Patent GB8208608, applied for in 1982, was assigned to National Research Development Corp UK and then British Technology Group, a British technology transfer organizing that was founded to commercialize publicly-funded research).[14] It was then developed at the University of Toronto in conjunction with Apotex. [15] Michael Spino, formerly a professor at the University of Toronto and then a part of Apotex, is named as an inventor on the Orange Book patent US7049328 that was assigned to Apotex.

[14] Quirke V, Judy Slinn. *Perspectives on Twentieth-Century Pharmaceuticals 1st Edition*. Peter Lang AG, Internationaler Verlag der Wissenschaften; 2010. pp323.
[15] Viens AM, Savulescu J. Introduction to The Olivieri symposium. J Med Ethics. 2004;30(1):1

INGENOL MEBUTATE	National Cancer Institute (US)/ University of Queensland (Australia)	Patent, AdisInsight, Drug History	The anti-cancer properties of ingenol was first described by Hasler et al. at the National Cancer Institute.[16] Jim Aylward and Peter Parsons at the Queensland Institute of Medical Research tested acetyl ingenol angelate for anti-melanoma activity in 1998 and established the company Peplin Biotech. The research was supported by Australian government grants.[17]
IVACAFTOR	Cystic Fibrosis Foundation Therapeutics	AdisInsight	Vertex initiated its cystic fibrosis research program in collaboration with Cystic Fibrosis Foundation Therapeutics, the non-profit drug discovery and development affiliated of the Cystic Fibrosis Foundation. Ivacaftor was discovered by Vertex as a part of this collaboration.[18] The Cystic Fibrosis Foundation controlled rights over the sales of ivacafator and sold its revenue rights for $3.3 billion.[19]
LUCINACTANT	The Scripps Research Institute	Patent	Orange Book patents: US 5407914 (assigned to The Scripps Research Institute).

[16] Hasler CM, Acs G, Blumberg PM. Specific binding to protein kinase C by ingenol and its induction of biological responses. Cancer Res. 1992;52(1):202-208.
[17] National Health and Medical Research Council. *Picato ® (Ingenol Mebutate) Gel: Case Study*. 2018. https://www.nhmrc.gov.au/sites/default/files/documents/Case%20studies/Case-Studies-Picato-Gel.pdf
[18] Vertex Pharmaceuticals Incorporated Investors.. FDA Approves KALYDECO ® (ivacaftor) as First and Only CFTR Modulator to Treat Eligible Infants with CF as Early as Six Months of Age Investors. Accessible at: https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecor-ivacaftor-first-and-only-cftr-modulator . Published April 30, 2019. Accessed August 8, 2019.
[19] Walker J, Rockoff JD. Cystic Fibrosis Foundation Sells Drug's Rights for $3.3 Billion. *The Wall Street Journal*. https://www.wsj.com/articles/cystic-fibrosis-foundation-sells-drugs-rights-for-3-3-billion-1416414300. Published November 19, 2014.

FLORBETAPIR F-18	University of Pennsylvania (NIH)	Patent	Orange Book patents: US7687052 and US8506929 (assigned to University of Pennsylvania) The US government retains rights on each of those patents (NIH grants AG-021868 and AG-022559).
COBICISTAT; ELVITEGRAVIR; EMTRICITABINE***; TENOFOVIR DISOPROXIL FUMARATE	Emory University (NIH)	Patent	Orange Book patents: US5814639, US5914331, US6642245 US6703396 on emtricitabine component (assigned to Emory University). The US government retains rights on each of those patents (NIH grants AI-26055; AI-28731; NIH 5-21935 and Veteran's Administration Merit Review Award).
ENZALUTAMIDE	University of California (US Army, NIH)	Patent	Orange Book patents: US 7709517, 8183274, 9126941 (assigned to The Regents of the University of California) The US government retains rights on each of these patents (NIH grant CA092131, SPORE grant 5 P50 CA092131; Department of Army grant W81XWH-04-1-0129)
CHOLINE C-11	Mayo Clinic	Drug History	Mayo Clinic received FDA approval in 2012 to produce and administer Choline C-11 injections for the detection of prostate

			cancer. Mayo Clinic is currently the only institution in North America approved to produce this imaging agent.[20]
TEDUGLUTIDE RECOMBINANT	Toronto General Hospital; University of Toronto	Patent, AdisInsight	Orange Book patents: US 5789379 to 1149336 Ontario Inc (a legal entity of Prof. Daniel Drucker of the University of Toronto). Teduglitide came out the work on GLPs by. Daniel Drucker first at the Habner lab in Boston and then through further investigation at the University of Toronto. Allelix then partnered with the University of Toronto with development of teduglutide.[21,22]
LOMITAPIDE MESYLATE	University of Pennsylvania	Patent	Orange Book patents: US 7932268, 8618135, 9265758, 9364470, 9433617, 9861622 (all assigned to University of Pennsylvania).
ALOGLIPTIN BENZOATE	University of Toronto, Tufts College, New England Medical Center Hospitals (NIH)	Patent	Orange Book patents: US 6890898, 7078381, 7459428 assigned variously to the Trustees of Tufts College, New England Medical Center Hospitals, and 1149336 Ontario Inc (a spin-off of University of Toronto led by Daniel Drucker). These patents are on methods of regulating glucose related to DPP-4.

[20] Mayo Foundation for Medical Education and Research (MFMER). MAYO CLINIC GETS APPROVAL FOR NEW PROSTATE CANCER IMAGING AGENT. *Forefront*. 2013:Volume 2, Issue 1. https://www.mayo.edu/research/forefront/mayo-clinic-gets-approval-new-prostate-cancer-imaging-agent.

[21] Drucker DJ, Habener JF, Holst JJ. Discovery, characterization, and clinical development of the glucagon-like peptides. J Clin Invest. 2017;127(12):4217-4227. doi:10.1172/JCI97233

[22] Drucker DJ. The Discovery of GLP-2 and Development of Teduglutide for Short Bowel Syndrome. ACS Pharmacol Transl Sci. 2019;2(2):134-142. doi:10.1021/acsptsci.9b00016

			The US government retains rights on each of those patents (NIH funding).
TECHNETIUM TC-99M TILMANOCEPT	University of California – San Diego (NIH)	Patent	Orange Book patents: US 6409990 assigned to The Regents of the University of California. The US government retains rights on the patent (NIH grant R01-CA72751).
FLUTEMETAMOL F-18	University of Pittsburgh	Patent	Orange Book patents: US 7270800, 7351401, 8236282, 8691185 assigned to University of Pittsburgh.
MILTEFOSINE	Max Planck Institute (Germany)	Patent (Merck index)	Merck Index Patent: US 4837023 to the Max Planck Institute
FLORBETABEN F-18	University of Pennsylvania (NIH)	Patent	Orange Book patent: US 7807135 assigned The Trustees of the University of Pennsylvania. The US government retains rights on the patent (NIH grant AG021868)
ELIGLUSTAT TARTRATE	University of Michigan (NIH)	Patent	Orange Book patents: US 6916802 assigned to University of Michigan. The US government retains rights on the patent (NIH grant R01 DK41487, R01 DK69255 and RO139255; NCI grants R43 CA 58159 and 2P30 CA 46592 via the University of Michigan Comprehensive

			Cancer Center; GMS grant GM 35712; Merit Award from Veteran's Administration).
OLAPARIB	University of Sheffield/Yorkshire Cancer Research/The Institute of Cancer Research/University of Cambridge (UK)	Patent, AdisInsight	Orange Book patents: US 7151102, ,7449464, 7981889, 8143241, 8247416, 8859562, 8912187 all to Kudus Pharmaceuticals (spin-off from University of Cambridge professor Steve Jackson) as well as The Institute of Cancer Research (8143241) and University Of Sheffield (8859562). Discovery at University of Sheffield and funding provided by the Yorkshire Cancer Research.[23]
PERAMIVIR	University of Alabama-Birmingham	Patent, AdisInsight	Orange Book patents: US 6503745, 6562861, 8778997 to BioCryst Pharmaceuticals. Discovery of the crystal structures of influenza neuroaminidase by Ming Luo and colleagues in the 1980s at University of Alabama – Birmingham (US 5453533), which was later licensed to BioCryst (a spinoff found by UAB faculty). Development was conducted in collaboration between BioCryst and UAB.[24]

[23] University of Sheffield. Pioneering new therapy discovered by Sheffield scientists approved for breast cancer patients. https://www.sheffield.ac.uk/news/nr/lynparza-breast-cancer-brca-new-therapy-1.757198. Published 2018. Accessed August 8, 2019.

[24] Williams, Greg. Bird flu: to fear and not to fear. The University of Alabama – Birmingham. April 30, 2013. Accessed August 8, 2019. The relevant section: "Note: BioCryst and UAB have had a close relationship since BioCryst was founded. Former BioCryst CEO, Dr. Charles E. Bugg, was also a past director of the UAB Center for Macromolecular Crystallography. Former BioCryst CEO, Dr. J. Claude Bennett, was previously UAB President. Several of BioCryst's early drug development programs originated at UAB. Currently, BioCryst has research agreements in place with UAB focused on influenza neuraminidase and complement inhibitors."

DEOXYCHOLIC ACID	University of California – Los Angeles	Patent	Orange Book patents: US 7622130, 7754230, 8101593, 8242294, 8298556, 8367649, 8461140, 8546367, 8653058, 8846066 to The Regents of the University of California and Los Angeles Biomed. Res. Inst. at Harbor UCLA Medical Center. US 8101593, 8242294, 8298556, 8367649, 8461140, 8546367, 8653058, 8846066, 8883770, 9522155, 9636349 to Kythera Biopharmaceuticals (spin-off from UCLA).
IVACAFTOR; LUMACAFTOR	Cystic Fibrosis Foundation Therapeutics	AdisInsight	Vertex initiated its cystic fibrosis research program in collaboration with Cystic Fibrosis Foundation Therapeutics, the non-profit drug discovery and development affiliated of the Cystic Fibrosis Foundation. Orkambi (lumacaftor/ivacaftor) was discovered by Vertex as a part of this collaboration. See the lumacaftor entry for further details.
TRABECTEDIN	University of Illinois	AdisInsight	Trabectedin is a tetrahydroisoquinoline alkaloid derived from the Caribbean marine tunicate, *E. turbinata*. The drug was synthetically isolated and developed by the University of Illinois and licensed to PharmaMar, which partnered with Johnson & Johnson to continue the R&D.[25,26]

[25] Trabectedin: Ecteinascidin 743, Ecteinascidin-743, ET 743, ET-743, NSC 684766. Drugs R D. 2006;7(5):317-328. doi:10.2165/00126839-200607050-00005
[26] Rinehart KL. Antitumor compounds from tunicates. Med Res Rev. 2000;20(1):1-27

COBICISTAT; ELVITEGRAVIR; EMTRICITABINE****; TENOFOVIR ALAFENAMIDE FUMARATE	Emory (NIH)	Patent	Orange Book patents: US 5814639, 5914331, 6642245 US6703396 on emtricitabine component (assigned to Emory University). The US government retains rights on each of those patents (NIH grants AI-26055; AI-28731; NIH 5-21935 and Veteran's Administration Merit Review Award).
VENETOCLAX	The Walter and Eliza Hall Institute of Medical Research	Patent	Orange Book patent: US 9174982 assigned to The Walter and Eliza Hall Institute of Medical Research.
FLUCICLOVINE F-18	Emory University (Department of Energy)	Patent	Orange Book patent: US 5808146 assigned to Emory University. The US government retains rights on the patent (Department of Energy Grant No. DE-FG05-93ER61737).
OBETICHOLIC ACID	University of Perugia (Italy)	Patent, AdisInsight	Obeticholic acid was discovered through a research program of Prof. Roberto Pellicciari of the University of Perugia, with first publication of its mechanism as selective ligand for the bile acid sensor, farnesoid-X-receptor in 2004.[27] Prof. Roberto Pellicciari co-founded Intercept Pharmaceuticals which developed the drug, with patent rights transferred to the company.[28]

[27] Pellicciari, R. , Pruzanski, M. and Gioiello, A. (2019). The Discovery of Obeticholic Acid (Ocaliva™): First- in- Class FXR Agonist. In Successful Drug Discovery (eds J. Fischer, C. Klein and W. E. Childers). doi:10.1002/9783527808694.ch8

[28] Intercept Pharmaceuticals, Inc. (2016). *Form 10-K 2016.* Retrieved from SEC EDGAR website: https://www.sec.gov/Archives/edgar/data/1270073/000114420417012180/v456571_10k.htm. Accessed August 8, 2019.

ETEPLIRSEN	Leiden University Medical Center (Netherlands)/University of Western Australia	Patent	Orange Book patents: US 8486907, 9018368 to The University of Western Australia and US 9243245 to Leiden University Medical Center.
RUCAPARIB CAMSYLATE	Newcastle University (UK)/Cancer Research UK	Patent	Orange Book patents: US 6495541, 7351701, 7531530, 8071579, 8143241, 8754072, 8859562 assigned variously to Cancer Research Technology Ltd., The Institute of Cancer Research, and University of Sheffield. Discovery a collaborative effort between Newcastle University and Cancer Research UK[27].
NUSINERSEN SODIUM	University of Massachusetts (NIH)/ Cold Spring Harbor Laboratory	Patent	Orange Book patents: US 7838657, 8110560 to the University of Massachusetts. US 8361977, 8980853, 9717750 to Cold Spring Harbor Laboratory. The US government retains rights on some of the patents (NIH grant ROI NS40275).
MIDOSTAURIN	Dana Farber Cancer Institute	Patent	Orange Book patents: US 7973031, 8222244 to Dana Farber Cancer Institute.
BENZNIDAZOLE	Brazilian Government, Drugs for Neglected Diseases	Drug History	Benzinidazole was discovered through research at Hoffman-LaRoche and not through publicly-supported research. However, Hoffman-

	Initiative Foundation		LaRoche donated the rights to the drug to the Brazilian government. In addition, the Drug for Neglected Diseases Initiative Foundation supported the development and FDA-approval of the drug in the US and is being sold on a "no profit no loss" basis.[29,30]
NETARSUDIL DIMESYLATE	Duke University	Patent, AdisInsight	Orange book patents: US 8394826, 8450344, 9096569, 9415043 to Aerie Pharmaceutical, a spin-off of Duke University based on collaboration by Duke University professors Dr. Eric Toone and Dr. David Epstein.[31]
ANGIOTENSIN II ACETATE	George Washington University	Patent	Orange Book patents: US 9220745, 9572856, 9867863 to The George Washington University.

[29] Food and Drug Administration. Combined Cross-Discipline Team Leader Review, Division Director, and Deputy Office Director Summary Review NDA 209570 Benznidazole. August 29, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209570Orig1s000SumR.pdf . Accessed August 8, 2019.

[30] Hernandez D. A New Strategy to Undermine Big Pharma's Price Gouging Actually Worked. Slate. 2017; (https://slate.com/technology/2017/09/inside-the-battle-to-approve-a-chagas-treatment.html)

[31] Howell WLJ. David Epstein, MD. Duke Innovation and Entrepreneurship Initiative. https://entrepreneurship.duke.edu/associate/david-epstein/%0A. Accessed August 8, 2019.

Table 2: New drugs with contributions from spin-off companies based on publicly-supported research

Drug Name (Generic)	Spin-off Company	Public-sector institution	Source	Rationale for Inclusion
ETRAVIRINE	Tibotec	Rega Institute	Patent, AdisInsight	Both etravirine and rilpivirine are nonnucleoside reverse transcriptase inhibitors and are successors to the TIBO compound discovered at the Rega Institute in 1987. This discovery led to the spin-off Tibotec, which was then bought by Johnson and Johnson and merged with its Janssen division).[32,33] The Orange Book patents identified (e.g. US 7037917) are assigned to Janssen.
IOFLUPANE I-123	Research Biochemicals International	Northeastern University	Patent	Orange Book patents: US 5310912 assigned to Research Biochemicals Limited Partnership, which was founded by Prof. John L. Neumeyer a researcher at Northeastern at the time (currently affiliated with Mclean Hospital).[34,35]
RILPIVIRINE HYDROCHLORIDE	Tibotec	Rega Institute	Patent, AdisInsight	Both etravirine and rilpivirine are nonnucleoside reverse transcriptase inhibitors and are successors to the TIBO compound discovered at the

[32] Janssen PA, Lewi PJ, Arnold E, et al. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2- pyrimidinyl]amino]benzonitrile (R278474, rilpivirine). J Med Chem. 2005;48(6):1901-1909. doi:10.1021/jm040840e

[33] Pauwels R, Andries K, Desmyter J, et al. Potent and selective inhibition of HIV-1 replication in vitro by a novel series of TIBO derivatives. Nature. 1990;343(6257):470-474. doi:10.1038/343470a0.

[34] Zhang A, Neumeyer JL, Baldessarini RJ. Recent Progress in Development of Dopamine Receptor Subtype-Selective Agents: Potential Therapeutics for Neurological and Psychiatric Disorders. Chem Rev. 2007;107(1):274-302. doi:10.1021/cr050263h

[35] MEDI Hall of Fame Inductees. American Chemical Society. https://www.acsmedchem.org/?nd=Neumeyer. Accessed August 8, 2019.

				Rega Institute in 1987. This discovery led to the spin-off Tibotec, which was then bought by Johnson and Johnson and merged with its Janssen division). The patents identified (e.g. US 7125879) are assigned to Janssen.
VEMURAFENIB	Plexxikon	Yale University / University of California-Berkeley.	Patent	Orange Book patents: US 7504509, 7863288, 8143271, 8470818 assigned to Plexxikon Inc, which was co-founded in 2001 by Joseph Schlessinger of Yale University with Sung-Hou Kim of the University of California, Berkeley, uses a proprietary structural biology-based platform called Scaffold-Based Drug Discovery[36] to build a pipeline of products in multiple therapeutic areas,[37] which led to the discovery of vemurafenib.[38]
CARFILZOMIB	Proteolix	Yale University / California Institute of Technology	Patent	Orange Book patents: US 7232818, 7417042, 7491704 to Proteolix, which was founded in 2003 based on technology developed by co-founders Dr. Craig Crews (Yale University) and Dr. Raymond J. Deshaies (California Institute of Technology).[39]
LINACLOTIDE	Microbia	Massachusetts	Patent	Orange Book patents: US 7304036, 7371727 to Microbia (later became

[36] Zhang KYJ, Card GL, Suzuki Y, et al. A glutamine switch mechanism for nucleotide selectivity by phosphodiesterases. Mol Cell. 2004;15(2):279-286. doi:10.1016/j.molcel.2004.07.005.
[37] About the Principal Investigator. Schlessinger Lab. https://medicine.yale.edu/lab/schlessinger/biography/. Accessed September 8, 2019.
[38] Tsai, James, et al. "Discovery of a selective inhibitor of oncogenic B-Raf kinase with potent antimelanoma activity." Proceedings of the National Academy of Sciences 105.8 (2008): 3041-3046.
[39] Carfilzomib/KyprolisTM. Crews Laboratory. http://crewslab.yale.edu/research/carfilzomibkyprolis/. Published 2017. Accessed August 8, 2019.

		Institute of Technology / Whitehead Institute		Ironwood Pharmaceuticals), which was founded in 1998 by postdocs from the lab of Gerald Fink at the Whitehead Institute to commercialize the use of fungi to produce of chemicals.[40]
RADIUM RA-223 DICHLORIDE	Anticancer Therapeutic Inventions	Norwegian Radium Hospital and the University of Oslo	Patent	Orange Book patent: US 6635234 to Anticancer Therapeutic Inventions AS (later Algeta), which is a spin-off of the Norwegian Radium Hospital and the University of Oslo founded by Roy Larsen and Øyvind S. Bruland based on research on alpha-emitting cancer therapeutics. [41]
SOFOSBUVIR	Pharmasset	Emory University	Patent	Orange Book patents: US 7964580 to Pharmasset (as well as many patents). Pharmasset was founded as a start-up company by Emory faculty members Raymond Schinazi and Dennis Liotta for treatment of hepatits C virus. Emory received Pharmasset stock as partial consideration for licensing various technologies to the company.[42]
TAVABOROLE	Anacor Pharmaceuticals	Stanford University/ Pennsylvania State	Patent	Orange Book patents: US 7582621, 7767657, 9549938, 9566289, 9566290, 9572823 to Anacor, which a spinoff of the work from Dr. Lucy Shapiro at Stanford University and Dr. Stephen Benkovic at

[40] Melissa Withers. DRUG HUNTERS. Whitehead Institute. http://wi.mit.edu/news/archive/2004/drug-hunters. Published 2004. Accessed August 8, 2019.
[41] Algeta in brief. Algeta Annual Report 2010. Available from: http://kundeweb.aggressive.no/users/algeta2.no/Annual%20Report%202010/algeta_in_brief.pdf . Accessed August 8th, 2019.
[42] Eastman Q, Korschun H. Emory celebrates top biotech innovations. Emory News Center. http://news.emory.edu/stories/2012/03/tech_transfer_highlights/campus.html. Published March 20, 2012.

		University		Pennsylvania State University for a boron-based class of anti-microbial.[43]
LEDIPASVIR; SOFOSBUVIR	Pharmasset	Emory University	Patent	See sofosbuvir entry.
SOFOSBUVIR; VELPATASVIR	Pharmasset	Emory University	Patent	See sofosbuvir entry.
RIBOCICLIB SUCCINATE	Astex Therapeutics	University of Cambridge	Patent	Orange book patents: US 8324225, 8415355, 8685980, 9193732, 9416136 assigned to Astex Therapeutics. Founded in 1999, by University of Cambridge researchers Drs. Tom Blundell, Chris Abell, and Dr. Harren Jhoti based on x-ray crystallography and fragment-based drug discovery platform.[44,45]
DELAFLOXACIN MEGLUMINE	Melinta	Yale University	Patent	Orange book patents: RE 46617, 8497378, 8871938 to Rib-X and Melinta. Rib-X is a spinoff company founded by Yale University researcher Dr. Tomas Steitz based on ribosomal antibiotic targets. Rib-X changed its name to Melinta.[46]

[43] Azvolinsky A. The Cell's Integrated Circuit: A Profile of Lucy Shapiro. The Scientist Magazine®. https://www.the-scientist.com/profile/the-cells-integrated-circuit--a-profile-of-lucy-shapiro-64496. Published August 1, 2018.
[44] Brackley P. How Astex founder Dr Harren Jhoti has changed the drug discovery process. Cambridge Independent. https://www.cambridgeindependent.co.uk/business/how-astex-founder-dr-harren-jhoti-has-changed-the-drug-discovery-process-9050898/. Published June 27, 2018.
[45] ASTEX. Milner Therapeutics Institute. https://www.milner.cam.ac.uk/astex/. Accessed August 8, 2019.
[46] United States Securities and Exchange Commission. Form S-1: Rib-X Pharmaceuticals, Inc. https://www.sec.gov/Archives/edgar/data/1164994/000119312511322087/d255425ds1.htm. Accessed August 8, 2019.

SOFOSBUVIR; VELPATASVIR; VOXILAPREVIR	Pharmasset	Emory University	Patent	See sofosbuvir entry.

Supplementary Table S1: FDA approved drugs containing a new molecular entity, 2008-2017

Approval Date	Drug Name (Generic)	Manufacturer	App No.	Drug Class	FDA Approval Characteristics*	Data Source**
1/18/2008	ETRAVIRINE	JANSSEN R AND D	#022187	Infectious diseases	P, A	OB; M
2/29/2008	DESVENLAFAXINE SUCCINATE	WYETH PHARMS INC	#021992	Psychiatric	S	OB; M
3/20/2008	BENDAMUSTINE HYDROCHLORIDE	CEPHALON	#022249	Hematologic-Oncologic	P, O	OB; No M patent
4/10/2008	REGADENOSON	ASTELLAS	#022161	Diagnostic	S	OB; M
4/24/2008	METHYLNALTREXONE BROMIDE	SALIX PHARMS	#021964	Gastrointestinal	S, FIC	OB; M
5/20/2008	ALVIMOPAN	CUBIST PHARMS	#021775	Gastrointestinal	S	OB; M
6/23/2008	DIFLUPREDNATE	NOVARTIS PHARMS CORP	#022212	Ophthalmologic	P	OB; M
7/3/2008	GADOXETATE DISODIUM	BAYER HLTHCARE	#022090	Diagnostic	S	OB; M
8/1/2008	CLEVIDIPINE	CHIESI USA INC	#022156	Cardiologic	S	OB; M
8/15/2008	TETRABENAZINE	VALEANT PHARMS NORTH	#021894	Neurologic	P, O, FIC	No OB patent; M
9/19/2008	IOBENGUANE SULFATE I-123	GE HEALTHCARE	#022290	Diagnostic	P, O	No OB patent; M
10/8/2008	SILODOSIN	ALLERGAN SALES LLC	#022206	Genitourinary/ Renal	S	No OB patent; M
10/28/2008	LACOSAMIDE	UCB INC	#022253	Neurologic	S	OB; M
10/31/2008	FESOTERODINE FUMARATE	PFIZER	#022030	Genitourinary/ Renal	S	OB; M
11/14/2008	RUFINAMIDE	EISAI INC	#021911	Neurologic	S, O	OB; M
11/20/2008	TAPENTADOL HYDROCHLORIDE	DEPOMED INC	#022304	Neurologic	S	OB; M
11/20/2008	ELTROMBOPAG OLAMINE	NOVARTIS PHARMS CORP	#022291	Hematologic-Oncologic	P, O, A	OB; M
12/15/2008	PLERIXAFOR	GENZYME	#022311	Hematologic-Oncologic	P, O, FIC	OB; No M patent
12/22/2008	GADOFOSVESET TRISODIUM	LANTHEUS MEDCL	#021711	Diagnostic	S	OB; M
12/24/2008	DEGARELIX ACETATE	FERRING	#022201	Hematologic-	S	OB; M

				Oncologic		
1/14/2009	MILNACIPRAN HYDROCHLORIDE	ALLERGAN SALES LLC	#022256	Psychiatric	S	OB; M
2/13/2009	FEBUXOSTAT	TAKEDA PHARMS USA	#021856	Metabolic / Endocrine	S	OB; M
3/30/2009	EVEROLIMUS	NOVARTIS	#022334	Hematologic-Oncologic	P	OB; M
4/7/2009	ARTEMETHER***; LUMEFANTRINE***	NOVARTIS	#022268	Infectious diseases	P, O, FT, FIC	OB; M
4/9/2009	BENZYL ALCOHOL	SHIONOGI INC	#022129	Infectious diseases	S	OB; No M patent
5/6/2009	ILOPERIDONE	VANDA PHARMS INC	#022192	Psychiatric	S	OB; M
5/19/2009	TOLVAPTAN	OTSUKA AMERICA PHARM	#022275	Genitourinary/ Renal	S	OB; M
5/28/2009	BESIFLOXACIN HYDROCHLORIDE	BAUSCH AND LOMB	#022308	Ophthalmologic	S	OB; M
7/1/2009	DRONEDARONE HYDROCHLORIDE	SANOFI AVENTIS US	#022425	Cardiologic	P	OB; M
7/10/2009	PRASUGREL HYDROCHLORIDE	ELI LILLY AND CO	#022307	Cardiologic	P	OB; M
7/31/2009	SAXAGLIPTIN HYDROCHLORIDE	ASTRAZENECA AB	#022350	Metabolic/ Endocrine	S	OB; M
8/13/2009	ASENAPINE MALEATE	FOREST LABS LLC	#022117	Psychiatric	S	OB; M
8/21/2009	VIGABATRIN	LUNDBECK PHARMS LLC	#020427	Neurologic	S, O	No OB patent; M
9/8/2009	BEPOTASTINE BESILATE		#022288	Ophthalmologic	S	OB; M
9/11/2009	TELAVANCIN HYDROCHLORIDE	THERAVANCE BIOPHARMA	#022110	Infectious diseases	S	OB; M
9/24/2009	PRALATREXATE	ALLOS	#022468	Hematologic-Oncologic	P, O, A	OB; M
10/19/2009	PAZOPANIB HYDROCHLORIDE	NOVARTIS PHARMS CORP	#022465	Hematologic-Oncologic	S	OB; M
11/5/2009	ROMIDEPSIN	CELGENE	#022393	Hematologic-Oncologic	S, O	OB; M
11/16/2009	CAPSAICIN	ACORDA	#022395	Neurologic	S, O	OB; No M patent
1/22/2010	DALFAMPRIDINE	ACORDA	#022250	Neurologic	P, O, FIC	OB; No M patent
1/25/2010	LIRAGLUTIDE RECOMBINANT	NOVO NORDISK INC	#022341	Metabolic / Endocrine	S	OB; M

2/26/2010	VELAGLUCERASE ALFA	SHIRE HUMAN GENETIC	#022575	Metabolic / Endocrine	P, O	No OB patent; M
3/18/2010	CARGLUMIC ACID	ORPHAN EUROPE	#022562	Metabolic / Endocrine	P, O, FT, FIC	No OB patent; No M patent
3/30/2010	POLIDOCANOL	CHEMISCH FBRK KRSSLR	#021201	Dermatology	S	No OB patent; No M patent
5/6/2010	DIENOGEST***; ESTRADIOL VALERATE	BAYER HLTHCARE	#022252	Women's Health	S	OB; M
6/17/2010	CABAZITAXEL	SANOFI AVENTIS US	#201023	Hematologic-Oncologic	P	OB; M
7/28/2010	ALCAFTADINE	ALLERGAN	#022134	Ophthalmologic	S	OB; No M entry
8/13/2010	ULIPRISTAL ACETATE	LAB HRA PHARMA	#022474	Women's Health	S	OB; M
9/21/2010	FINGOLIMOD	NOVARTIS	#022527	Neurologic	P, FIC	OB; M
10/19/2010	DABIGATRAN ETEXILATE MESYLATE	BOEHRINGER INGELHEIM	#022512	Hematologic-Oncologic	P	OB; M
10/28/2010	LURASIDONE HYDROCHLORIDE	SUNOVION PHARMS INC	#200603	Psychiatric	S	OB; M
10/29/2010	CEFTAROLINE FOSAMIL	ALLERGAN SALES LLC	#200327	Infectious diseases	S	OB; M
11/10/2010	TESAMORELIN ACETATE	THERATECHNOLOGIES	#022505	Metabolic / Endocrine	S, FIC	OB; M
11/15/2010	ERIBULIN MESYLATE	EISAI INC	#201532	Hematologic-Oncologic	P, FIC	OB; M
1/14/2011	IOFLUPANE I-123	GE HLTHCARE INC	#022454	Diagnostic	P	OB; M
1/18/2011	SPINOSAD	PARAPRO LLC	#022408	Infectious diseases	S	OB; No M patent
1/21/2011	VILAZODONE HYDROCHLORIDE	ALLERGAN SALES LLC	#022567	Psychiatric	S	OB; M
2/25/2011	AZILSARTAN KAMEDOXOMIL	ARBOR PHARMS LLC	#200796	Cardiologic	S	OB; M
2/28/2011	ROFLUMILAST	ASTRAZENECA PHARMS	#022522	Pulmonary	S, FIC	OB; M
3/14/2011	GADOBUTROL	BAYER HLTHCARE	#201277	Diagnostic	S	OB; M
4/6/2011	VANDETANIB	GENZYME CORP	#022405	Hematologic-Oncologic	P, O, FT	OB; M
4/6/2011	GABAPENTIN ENACARBIL	ARBOR PHARMS LLC	#022399	Psychiatric	S	OB; M
4/28/2011	ABIRATERONE ACETATE	JANSSEN BIOTECH	#202379	Hematologic-Oncologic	P, FIC	OB; M

5/2/2011	LINAGLIPTIN	BOEHRINGER INGELHEIM	#201280	Metabolic / Endocrine	S	OB; M
5/13/2011	BOCEPREVIR	MERCK SHARP DOHME	#202258	Infectious diseases	P, FT, FIC	OB; M
5/20/2011	RILPIVIRINE HYDROCHLORIDE	JANSSEN PRODS	#202022	Infectious diseases	S	OB; M
5/23/2011	TELAPREVIR	VERTEX PHARMS	#201917	Infectious diseases	P, FT	OB; M
5/27/2011	FIDAXOMICIN	CUBIST PHARMS LLC	#201699	Infectious diseases	P, FT	OB; M
6/10/2011	EZOGABINE	GLAXOSMITHKLINE	#022345	Neurologic	S, FIC	No OB patent; M
7/1/2011	INDACATEROL MALEATE	SUNOVION PHARMS INC	#022383	Pulmonary	S	OB; M
7/1/2011	RIVAROXABAN	JANSSEN PHARMS	#022406	Hematologic-Oncologic	S	OB; M
7/20/2011	TICAGRELOR	ASTRAZENECA PHARMS	#022433	Cardiologic	S	OB; M
8/17/2011	VEMURAFENIB	HOFFMANN LA ROCHE	#202429	Hematologic-Oncologic	P, O, FT, FIC	OB; M
8/25/2011	ICATIBANT ACETATE	SHIRE ORPHAN THERAP	#022150	Hematologic-Oncologic	P, O, FT, FIC	OB; M
8/26/2011	CRIZOTINIB	PF PRISM CV	#202570	Hematologic-Oncologic	P, O, A, FT, FIC	OB; M
10/14/2011	DEFERIPRONE	APOPHARMA INC	#021825	Hematologic-Oncologic	S, O, A, FT	OB; No M patent
10/21/2011	CLOBAZAM	LUNDBECK PHARMS LLC	#202067	Neurologic	S, O	No OB patent; M
11/16/2011	RUXOLITINIB PHOSPHATE	INCYTE CORP	#202192	Hematologic-Oncologic	P, O, FT, FIC	OB; M
1/23/2012	INGENOL MEBUTATE	LEO LABS	#202833	Dermatology	S, FIC	OB; M
1/27/2012	AXITINIB	PF PRISM CV	#202324	Hematologic-Oncologic	S, FT	OB; M
1/30/2012	VISMODEGIB	GENENTECH	#203388	Hematologic-Oncologic	P, FIC	OB; M
1/31/2012	IVACAFTOR	VERTEX PHARMS	#203188	Pulmonary	P, O, FT, FIC	OB; M
2/10/2012	TAFLUPROST	OAK PHARMS INC	#202514	Ophthalmologic	S	OB; M
3/6/2012	LUCINACTANT	WINDTREE THERAP	#021746	Pulmonary	S, FT	OB; No M entry
3/27/2012	PEGINESATIDE ACETATE	TAKEDA PHARMS USA	#202799	Hematologic-Oncologic	S	OB; M
4/6/2012	FLORBETAPIR F-18	AVID RADIOPHARMS INC	#202008	Diagnostic	P, FIC	OB; M
4/27/2012	AVANAFIL	METUCHEN PHARMS	#202276	Genitourinary/	S	OB; M

				Renal		
5/1/2012	TALIGLUCERASE ALFA	PFIZER	#022458	Metabolic / Endocrine	S, O, FT	OB; M
6/27/2012	LORCASERIN HYDROCHLORIDE	EISAI INC	#022529	Metabolic / Endocrine	S, FIC	OB; M
6/28/2012	MIRABEGRON	APGDI	#202611	Genitourinary/ Renal	S, FIC	OB; M
7/16/2012	CITRIC ACID; MAGNESIUM OXIDE; SODIUM PICOSULFATE***	FERRING PHARMS INC	#202535	Gastrointestinal	S	OB; No M entry
7/20/2012	CARFILZOMIB	ONYX THERAP	#202714	Hematologic-Oncologic	S, O, A, FT	OB; M
7/23/2012	ACLIDINIUM BROMIDE	ASTRAZENECA PHARMS	#202450	Pulmonary	S	OB; M
8/27/2012	COBICISTAT; ELVITEGRAVIR***; EMTRICITABINE; TENOFOVIR DISOPROXIL FUMARATE	GILEAD SCIENCES INC	#203100	Infectious diseases	S, FT	OB; M
8/30/2012	LINACLOTIDE	ALLERGAN SALES LLC	#202811	Gastrointestinal	S, FIC	OB; M
8/31/2012	ENZALUTAMIDE	ASTELLAS	#203415	Hematologic-Oncologic	P, FT	OB; No M patent
9/4/2012	BOSUTINIB MONOHYDRATE	PF PRISM CV	#203341	Hematologic-Oncologic	S, O	OB; M
9/12/2012	TERIFLUNOMIDE	SANOFI AVENTIS US	#202992	Neurologic	S, FIC	OB; M
9/12/2012	CHOLINE C-11	MCPRF	#203155	Diagnostic	P, FIC	No OB patent; No M patent
9/27/2012	REGORAFENIB	BAYER HLTHCARE	#203085	Hematologic-Oncologic	P, FT	OB; M
10/22/2012	PERAMPANEL	EISAI INC	#202834	Neurologic	S, FIC	OB; M
10/26/2012	OMACETAXINE MEPESUCCINATE	TEVA PHARMS INTL	#203585	Hematologic-Oncologic	S, O, A, FIC	OB; M
11/6/2012	TOFACITINIB CITRATE	PF PRISM CV	#203214	Rheumatologic	S	OB; M
11/29/2012	CABOZANTINIB S-MALATE	EXELIXIS	#203756	Hematologic-Oncologic	P, O, FT, FIC	OB; M
12/14/2012	PONATINIB HYDROCHLORIDE	ARIAD	#203469	Hematologic-Oncologic	P, O, A, FT	OB; M

12/14/2012	PASIREOTIDE DIASPARTATE	NOVARTIS	#200677	Metabolic / Endocrine	S, O, FIC	OB; M
12/21/2012	TEDUGLUTIDE RECOMBINANT	NPS PHARMS INC	#203441	Gastrointestinal	S, O, FIC	OB; M
12/21/2012	LOMITAPIDE MESYLATE	AEGERION	#203858	Cardiologic	S, O, FIC	OB; No M patent
12/28/2012	APIXABAN	BRISTOL MYERS SQUIBB	#202155	Hematologic-Oncologic	P	OB; M
12/28/2012	BEDAQUILINE FUMARATE	JANSSEN THERAP	#204384	Infectious diseases	P, O, A, FT, FIC	OB; M
12/31/2012	CROFELEMER	NAPO PHARMS INC	#202292	Gastrointestinal	P, FT, FIC	OB; M
1/25/2013	ALOGLIPTIN BENZOATE	TAKEDA PHARMS USA	#022271	Metabolic / Endocrine	S	OB; M
1/29/2013	MIPOMERSEN SODIUM	KASTLE THERAPS LLC	#203568	Cardiologic	S, O, FIC	OB; M
2/8/2013	POMALIDOMIDE	CELGENE	#204026	Hematologic-Oncologic	S, O, A, FT	OB; M
2/26/2013	OSPEMIFENE	DUCHESNAY	#203505	Women's Health	S	OB; M
3/13/2013	TECHNETIUM TC-99M TILMANOCEPT	CARDINAL HEALTH 414	#202207	Diagnostic	S	OB; No M patent
3/20/2013	GADOTERATE MEGLUMINE	GUERBET	#204781	Diagnostic	P	No OB patent; M
3/27/2013	DIMETHYL FUMARATE	BIOGEN IDEC INC	#204063	Neurologic	S, FIC	OB; No M patent
3/29/2013	CANAGLIFLOZIN	JANSSEN PHARMS	#204042	Metabolic / Endocrine	S, FIC	OB; M
5/10/2013	FLUTICASONE FUROATE; VILANTEROL TRIFENATATE***	GLAXO GRP LTD	#204275	Pulmonary	S	OB; M
5/15/2013	RADIUM RA-223 DICHLORIDE	BAYER HLTHCARE	#203971	Hematologic-Oncologic	P, FT, FIC	OB; M
5/29/2013	TRAMETINIB DIMETHYL SULFOXIDE	NOVARTIS PHARMS CORP	#204114	Hematologic-Oncologic	S, O, FT, FIC	OB; M
5/29/2013	DABRAFENIB MESYLATE	NOVARTIS PHARMS CORP	#202806	Hematologic-Oncologic	S, O, FT	OB; M
7/12/2013	AFATINIB DIMALEATE	BOEHRINGER INGELHEIM	#201292	Hematologic-Oncologic	P, O, FT	OB; M
8/12/2013	DOLUTEGRAVIR SODIUM	VIIV HLTHCARE	#204790	Infectious diseases	P, FT	OB; M
9/30/2013	VORTIOXETINE	TAKEDA PHARMS USA	#204447	Psychiatric	S	OB; M

	HYDROBROMIDE					
10/3/2013	BAZEDOXIFENE ACETATE***; ESTROGENS, CONJUGATED	WYETH PHARMS PFIZER	#022247	Women's Health	S	OB; M
10/8/2013	RIOCIGUAT	BAYER HLTHCARE	#204819	Pulmonary	P, O, FIC	OB; M
10/18/2013	MACITENTAN	ACTELION PHARMS LTD	#204410	Pulmonary	S, O	OB; M
10/25/2013	FLUTEMETAMOL F-18	GE HEALTHCARE	#203137	Diagnostic	S	OB; M
11/8/2013	ESLICARBAZEPINE ACETATE	SUNOVION PHARMS INC	#022416	Neurologic	S	OB; M
11/13/2013	IBRUTINIB	PHARMACYCLICS INC	#205552	Hematologic-Oncologic	P, O, A, B, FT, FIC	OB; M
11/14/2013	LULICONAZOLE	MEDICIS	#204153	Infectious diseases	S	OB; M
11/22/2013	SIMEPREVIR SODIUM	JANSSEN PRODS	#205123	Infectious diseases	P, FT	OB; M
12/6/2013	SOFOSBUVIR	GILEAD SCIENCES INC	#204671	Infectious diseases	P, B, FT, FIC	OB; M
12/18/2013	UMECLIDINIUM BROMIDE***; VILANTEROL TRIFENATATE	GLAXOSMITHKLINE	#203975	Pulmonary	S	OB; M
1/8/2014	DAPAGLIFLOZIN	ASTRAZENECA AB	#202293	Metabolic / Endocrine	S	OB; M
1/31/2014	TASIMELTEON	VANDA PHARMS INC	#205677	Psychiatric	P, O	OB; M
2/18/2014	DROXIDOPA	LUNDBECK NA LTD	#203202	Cardiologic	P, O, A, FT, FIC	No OB patent; M
3/19/2014	MILTEFOSINE	KNIGHT THERAPS	#204684	Infectious diseases	P, O, FT, FIC	No OB patent; M
3/19/2014	FLORBETABEN F-18	PIRAMAL IMAGING	#204677	Diagnostic	S	OB; M
3/21/2014	APREMILAST	CELGENE CORP	#205437	Rheumatologic	S, FIC	OB; M
4/29/2014	CERITINIB	NOVARTIS PHARMS CORP	#205755	Hematologic-Oncologic	P, O, A, B	OB; M
5/8/2014	VORAPAXAR SULFATE	ARALEZ PHARMS	#204886	Cardiologic	S, FT, FIC	OB; M
5/23/2014	DALBAVANCIN HYDROCHLORIDE	ALLERGAN SALES LLC	#021883	Infectious diseases	P, FT	OB; No M patent
6/6/2014	EFINACONAZOLE	DOW PHARM	#203567	Dermatology	S	OB; M
6/20/2014	TEDIZOLID PHOSPHATE	CUBIST PHARMS LLC	#205435	Infectious diseases	P	OB; M
7/3/2014	BELINOSTAT	SPECTRUM PHARMS	#206256	Hematologic-Oncologic	P, O, A, FT	OB; M

7/7/2014	TAVABOROLE	ANACOR PHARMS INC	#204427	Dermatology	S, FIC	OB; M
7/23/2014	IDELALISIB	GILEAD SCIENCES INC	#205858	Hematologic-Oncologic	S, O, A, B, FT, FIC	OB; M
7/31/2014	OLODATEROL HYDROCHLORIDE	BOEHRINGER INGELHEIM	#203108	Pulmonary	S	OB; M
8/1/2014	EMPAGLIFLOZIN	BOEHRINGER INGELHEIM	#204629	Metabolic / Endocrine	S	OB; M
8/6/2014	ORITAVANCIN DIPHOSPHATE	MELINTA THERAP	#206334	Infectious diseases	P	OB; M
8/13/2014	SUVOREXANT	MERCK SHARP DOHME	#204569	Psychiatric	S, FIC	OB; M
8/19/2014	ELIGLUSTAT TARTRATE	GENZYME CORP	#205494	Metabolic / Endocrine	P, O	OB; M
9/16/2014	NALOXEGOL OXALATE	ASTRAZENECA PHARMS	#204760	Gastrointestinal	S	OB; No M entry
10/10/2014	NETUPITANT***; PALONOSETRON HYDROCHLORIDE	HELSINN HLTHCARE	#205718	Gastrointestinal	S	OB; M
10/10/2014	LEDIPASVIR***; SOFOSBUVIR	GILEAD SCIENCES INC	#205834	Infectious diseases	P, B, FT, FIC	OB; No M entry
10/10/2014	SULFUR HEXAFLUORIDE LIPID-TYPE A MICROSPHERES	BRACCO	#203684	Diagnostic	S	OB; No M patent
10/15/2014	PIRFENIDONE	GENENTECH INC	#022535	Pulmonary	P, O, B, FT, FIC	OB; M
10/15/2014	NINTEDANIB ESYLATE	BOEHRINGER INGELHEIM	#205832	Pulmonary	P, O, B, FT, FIC	OB; M
12/17/2014	FINAFLOXACIN	NOVARTIS PHARMS CORP	#206307	Infectious diseases	P	OB; M
12/19/2014	OLAPARIB	ASTRAZENECA PHARMS	#206162	Hematologic-Oncologic	P, O, A, FIC	OB; M
12/19/2014	PERAMIVIR	BIOCRYST	#206426	Infectious diseases	S, FT	OB; M
12/19/2014	DASABUVIR SODIUM***; OMBITASVIR***; PARITAPREVIR***; RITONAVIR	ABBVIE INC	#206619	Infectious diseases	P, B, FT, FIC	OB; M
12/19/2014	CEFTOLOZANE SULFATE***; TAZOBACTAM SODIUM	CUBIST PHARMS LLC	#206829	Infectious diseases	P, FT	OB; M
1/8/2015	EDOXABAN TOSYLATE	DAIICHI SANKYO INC	#206316	Hematologic-	S	OB; M

				Oncologic		
2/3/2015	PALBOCICLIB	PFIZER INC	#207103	Hematologic-Oncologic	P, A, B, FIC	OB; M
2/13/2015	LENVATINIB MESYLATE	EISAI INC	#206947	Hematologic-Oncologic	P, O	OB; M
2/23/2015	PANOBINOSTAT LACTATE	NOVARTIS PHARMS CORP	#205353	Hematologic-Oncologic	P, O, A	OB; M
2/25/2015	AVIBACTAM SODIUM***; CEFTAZIDIME	ALLERGAN SALES LLC	#206494	Infectious diseases	P, FT	OB; No M entry
3/6/2015	ISAVUCONAZONIUM SULFATE	ASTELLAS	#207500	Infectious diseases	P, O	OB; M
3/17/2015	CHOLIC ACID	RTRX	#205750	Gastrointestinal	P, O	No OB patent; No M entry
4/15/2015	IVABRADINE HYDROCHLORIDE	AMGEN INC	#206143	Cardiologic	P, FT, FIC	OB; M
4/29/2015	DEOXYCHOLIC ACID	KYTHERA BIOPHARMS	#206333	Dermatology	S	OB; M
5/27/2015	ELUXADOLINE	ALLERGAN HOLDINGS	#206940	Gastrointestinal	P, FT	OB; M
6/22/2015	CANGRELOR	CHIESI USA INC	#204958	Cardiologic	S	OB; M
7/2/2015	IVACAFTOR; LUMACAFTOR***	VERTEX PHARMS INC	#206038	Pulmonary	P, O, B, FT, FIC	OB; No M entry
7/7/2015	SACUBITRIL***; VALSARTAN	NOVARTIS PHARMS CORP	#207620	Cardiologic	P, FT, FIC	OB; No M entry
7/10/2015	BREXPIPRAZOLE	OTSUKA PHARM CO LTD	#205422	Psychiatric	S	OB; M
7/24/2015	DACLATASVIR DIHYDROCHLORIDE	BRISTOL-MYERS SQUIBB	#206843	Infectious diseases	P, FT	OB; M
7/24/2015	SONIDEGIB PHOSPHATE	SUN PHARMA GLOBAL	#205266	Hematologic-Oncologic	S	OB; M
8/18/2015	FLIBANSERIN	SPROUT PHARMS	#022526	Women's Health	S, FIC	OB; M
9/1/2015	ROLAPITANT HYDROCHLORIDE	TESARO INC	#206500	Gastrointestinal	S	OB; No M patent
9/4/2015	URIDINE TRIACETATE	WELLSTAT THERAP	#208169	Metabolic / Endocrine	P, O, B, FIC	OB; M
9/17/2015	CARIPRAZINE HYDROCHLORIDE	ALLERGAN SALES LLC	#204370	Psychiatric	S	OB; M
9/22/2015	TIPIRACIL HYDROCHLORIDE***; TRIFLURIDINE	TAIHO ONCOLOGY	#207981	Hematologic-Oncologic	S, FT	OB; No M entry

9/25/2015	INSULIN DEGLUDEC	NOVO NORDISK INC	#203314	Metabolic / Endocrine	S	OB; M
10/5/2015	ARIPIPRAZOLE LAUROXIL	ALKERMES INC	#207533	Psychiatric	S	OB; M
10/21/2015	PATIROMER SORBITEX CALCIUM	RELYPSA INC	#205739	Gastrointestinal	S	OB; M
10/23/2015	TRABECTEDIN	JANSSEN PRODS	#207953	Hematologic-Oncologic	P, O	OB; No M entry
11/5/2015	COBICISTAT; ELVITEGRAVIR; EMTRICITABINE; TENOFOVIR ALAFENAMIDE FUMARATE***	GILEAD SCIENCES INC	#207561	Infectious diseases	S, FT	OB; M
11/10/2015	COBIMETINIB FUMARATE	GENENTECH INC	#206192	Hematologic-Oncologic	P, O, FT	OB; M
11/13/2015	OSIMERTINIB MESYLATE	ASTRAZENECA PHARMS	#208065	Hematologic-Oncologic	P, O, A, B, FT	OB; M
11/20/2015	IXAZOMIB CITRATE	MILLENNIUM PHARMS	#208462	Hematologic-Oncologic	P, O	OB; M
12/11/2015	ALECTINIB HYDROCHLORIDE	HOFFMANN-LA ROCHE	#208434	Hematologic-Oncologic	P, O, A, B	OB; M
12/15/2015	SUGAMMADEX SODIUM	ORGANON SUB MERCK	#022225	Anesthesia	P, FIC	OB; M
12/21/2015	SELEXIPAG	ACTELION PHARMS LTD	#207947	Pulmonary	S, O	OB; M
12/22/2015	LESINURAD	IRONWOOD PHARMS INC	#207988	Metabolic / Endocrine	S	OB; M
1/28/2016	ELBASVIR***; GRAZOPREVIR***	MERCK SHARP DOHME	#208261	Infectious diseases	P, B	OB; M
2/18/2016	BRIVARACETAM	UCB INC	#205836	Neurologic	S	OB; M
3/30/2016	DEFIBROTIDE SODIUM	JAZZ PHARMS INC	#208114	Hematologic-Oncologic	P, O, FT, FIC	No OB patent; M
4/11/2016	VENETOCLAX	ABBVIE INC	#208573	Hematologic-Oncologic	P, O, A, B, FIC	OB; M
4/29/2016	PIMAVANSERIN TARTRATE	ACADIA PHARMS INC	#207318	Psychiatric	P, B	OB; M
5/27/2016	FLUCICLOVINE F-18	BLUE EARTH	#208054	Diagnostic	P	OB; No M entry
5/27/2016	OBETICHOLIC ACID	INTERCEPT PHARMS INC	#207999	Gastrointestinal	P, O, A, FT, FIC	OB; M

6/1/2016	GALLIUM DOTATATE GA-68	AAA USA INC	#208547	Diagnostic	P, O	No OB patent; M
6/28/2016	SOFOSBUVIR; VELPATASVIR***	GILEAD SCIENCES INC	#208341	Infectious diseases	P, B, FT	OB; M
7/11/2016	LIFITEGRAST	SHIRE DEV LLC	#208073	Ophthalmologic	P, FIC	OB; M
7/27/2016	LIXISENATIDE	SANOFI-AVENTIS US	#208471	Metabolic / Endocrine	S	OB; M
9/19/2016	ETEPLIRSEN	SAREPTA THERAPS INC	#206488	Neurologic	P, O, A, FT, FIC	OB; No M entry
12/14/2016	CRISABOROLE	ANACOR PHARMS INC	#207695	Dermatology	S	OB; M
12/19/2016	RUCAPARIB CAMSYLATE	CLOVIS ONCOLOGY INC	#209115	Hematologic-Oncologic	P, O, A, B	OB; M
12/23/2016	NUSINERSEN SODIUM	BIOGEN IDEC	#209531	Neurologic	P, O, FT, FIC	OB; M
1/19/2017	PLECANATIDE	SYNERGY PHARMS	#208745	Gastrointestinal	S	OB; M
2/7/2017	ETELCALCETIDE	KAI PHARMS INC	#208325	Metabolic / Endocrine	S	OB; M
2/9/2017	DEFLAZACORT	PTC THERAP	#208684	Neurologic	P, O, FT, FIC	No OB patent; M
2/28/2017	TELOTRISTAT ETIPRATE	LEXICON PHARMS INC	#208794	Gastrointestinal	P, O, FT, FIC	OB; M
3/13/2017	RIBOCICLIB SUCCINATE	NOVARTIS PHARMS CORP	#209092	Hematologic-Oncologic	P, B	OB; M
3/21/2017	SAFINAMIDE MESYLATE	US WORLDMEDS LLC	#207145	Neurologic	S	OB; M
3/23/2017	NALDEMEDINE TOSYLATE	SHIONOGI INC	#208854	Gastrointestinal	S	OB; M
3/27/2017	NIRAPARIB TOSYLATE	TESARO INC	#208447	Hematologic-Oncologic	P, O, B, FT	OB; M
4/3/2017	DEUTETRABENAZINE	TEVA BRANDED PHARM	#208082	Neurologic	S, O	OB; No M entry
4/11/2017	VALBENAZINE TOSYLATE	NEUROCRINE	#209241	Psychiatric	P, B, FT	OB; M
4/28/2017	BRIGATINIB	ARIAD	#208772	Hematologic-Oncologic	P, O, A, B	OB; No M entry
4/28/2017	MIDOSTAURIN	NOVARTIS PHARMS CORP	#207997	Hematologic-Oncologic	P, O, B, FT, FIC	OB; M
4/28/2017	ABALOPARATIDE	RADIUS HEALTH INC	#208743	Women's Health	S	OB; M
5/5/2017	EDARAVONE	MITSUBISHI TANABE	#209176	Neurologic	S, O, FIC	OB; No M patent
6/19/2017	DELAFLOXACIN MEGLUMINE	MELINTA	#208610	Infectious diseases	P, FT	OB; M

6/23/2017	BETRIXABAN	PORTOLA PHARMS INC	#208383	Hematologic-Oncologic	P, FT	OB; M
7/17/2017	NERATINIB MALEATE	PUMA BIOTECH	#208051	Hematologic-Oncologic	S	OB; M
7/18/2017	SOFOSBUVIR; VELPATASVIR; VOXILAPREVIR***	GILEAD SCIENCES INC	#209195	Infectious diseases	P, FT	OB; M
8/1/2017	ENASIDENIB MESYLATE	CELGENE CORP	#209606	Hematologic-Oncologic	P, O, FT, FIC	OB; No M entry
8/3/2017	GLECAPREVIR***; PIBRENTASVIR***	ABBVIE INC	#209394	Infectious diseases	P, B, FT	OB; M
8/29/2017	BENZNIDAZOLE	CHEMO RESEARCH SL	#209570	Infectious diseases	P, O, A	No OB patent; M
8/29/2017	MEROPENEM; VABORBACTAM***	REMPEX PHARMS	#209776	Infectious diseases	P, FT	OB; M
9/14/2017	COPANLISIB DIHYDROCHLORIDE	BAYER HEALTHCARE	#209936	Hematologic-Oncologic	P, O, A, FT	OB; M
9/15/2017	SECNIDAZOLE	LUPIN	#209363	Infectious diseases	P, FT	No OB patent; M
9/28/2017	ABEMACICLIB	ELI LILLY AND CO	#208716	Hematologic-Oncologic	P, B, FT	OB; M
10/31/2017	ACALABRUTINIB	ASTRAZENECA	#210259	Hematologic-Oncologic	P, O, A, B	OB; M
11/2/2017	LATANOPROSTENE BUNOD	BAUSCH AND LOMB	#207795	Ophthalmologic	S	OB; No M entry
11/8/2017	LETERMOVIR	MERCK SHARP DOHME	#209939	Infectious diseases	P, O, B, FT, FIC	OB; No M entry
12/5/2017	SEMAGLUTIDE	NOVO NORDISK INC	#209637	Metabolic / Endocrine	S	OB; No M entry
12/11/2017	OZENOXACIN	FERRER INTERNACIONAL	#208945	Infectious diseases	S	OB; M
12/18/2017	NETARSUDIL DIMESYLATE	AERIE PHARMS INC	#208254	Ophthalmologic	S, FIC	OB; No M entry
12/19/2017	ERTUGLIFLOZIN	MERCK SHARP DOHME	#209803	Metabolic / Endocrine	S	OB; No M entry
12/20/2017	MACIMORELIN ACETATE	STRONGBRIDGE IRELAND	#205598	Diagnostic	S, O, FIC	OB; No M entry
12/21/2017	ANGIOTENSIN II ACETATE	LA JOLLA PHARM CO	#209360	Cardiologic	P, FIC	OB; No M patent

*Represents designations by the Food and Drug Administration (FDA) as follows: S – standard approval, P – priority approval, O – orphan drug designation, A – accelerated approval, B – breakthrough designation, FT – fast track designation, FIC – first in class.

**OB – At least one patent listed in the FDA Orange Book. M – At least one patent listed in the drug's Merck Index entry. AdisInsight entries were available for all drugs except citric acid/magnesium oxide/sodium picosulfate (prepopik) and choline C-11.

***Identifies the new molecular entity for combination products.

Supplementary Table S2: New approvals and origins by drug class

Drug Class	Publicly-supported	Publicly-supported spin-off	Public-sector and spin-off total	Total Approvals
Diagnostic	9	1	10	16
Anesthetic	0	0	0	1
Cardiologic	2	0	2	13
Dermatologic	2	1	3	6
Gastrointestinal	3	1	4	16
Genitourinary/Renal	0	0	0	5
Hematologic-Oncologic	13	4	17	64
Infectious diseases	6	7	13	39
Metabolic/Endocrine	3	0	3	22
Neurologic	5	0	5	21
Ophthalmologic	1	0	1	8
Psychiatric	0	0	0	15
Pulmonary	3	0	3	14
Rheumatologic	0	0	0	2
Women's health	1	0	1	6
Total	**48**	**14**	**62**	**248**