

By Aaron S. Kesselheim, Yongtian Tina Tan, and Jerry Avorn

DOI: 10.1377/hlthaff.2014.1038
HEALTH AFFAIRS 34,
NO. 2 (2015): 286-293
©2015 Project HOPE—
The People-to-People Health
Foundation, Inc.

The Roles Of Academia, Rare Diseases, And Repurposing In The Development Of The Most Transformative Drugs

Aaron S. Kesselheim

(akesselheim@partners.org) is an associate professor of medicine at Harvard Medical School, in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital, in Boston, Massachusetts.

Yongtian Tina Tan is a medical student at Harvard Medical School.

Jerry Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital.

ABSTRACT Transformative drugs, defined as pharmaceuticals that are both innovative and have groundbreaking effects on patient care, are the “holy grail” of drug research and development. The sources of drug innovation are often debated, with pharmaceutical manufacturers arguing that high drug prices support innovative output from their sector. We studied the developmental histories of twenty-six drugs or drug classes approved by the Food and Drug Administration between 1984 and 2009 that were judged by expert physicians to be transformative (in two cases, the first drug in a transformative class was approved before 1984). Most of the twenty-six were first approved early in the study period; only four were approved in 2000 or later. Many were based on discoveries made by academic researchers who were supported by federal government funding. Others were jointly developed in both publicly funded and commercial institutions; the fewest number of drugs had originated solely within pharmaceutical industry research programs. Nine of the twenty-six (35 percent) were repurposed from products developed for other indications, and ten (38 percent) were developed for rare diseases before much broader applicability was found. The insights from these case studies provide an experience-based foundation for policies to encourage the development of future transformative drugs.

Much attention has been paid to the perceived decline in the number of new innovative products emerging from an increasingly cost-intensive drug development process. Recent advances in biomedicine, such as those based on genetics and molecular biology approaches, have not yet produced the large number of anticipated new therapeutic breakthroughs. Total research and development expenditures have increased. However, the rate of introduction of new molecular entities or novel drugs in the past decade has been in line with or slightly above the rate observed in the 1970s and 1980s, with continued substantial attrition in late-phase clinical trials.¹

In response, investigators have tried to identify factors that explain the successes and limits of drug innovation.² Some analyses have concluded that the pharmaceutical industry is the most important source of new drugs, while others have concluded that academic research is the key driver of important innovation that leads to new pharmaceutical products.³

Most studies of pharmaceutical innovation are limited because they focus on all approved drugs, not only those that are truly innovative. For example, the drug discovery and development process that led to the first HMG-CoA reductase inhibitor (statin) to lower cholesterol—lovastatin (Mevacor)—differed substantially from the steps that led to the development of products

that followed this innovative one, such as atorvastatin (Lipitor). Although atorvastatin was the biggest blockbuster drug of the past decade, it would not have existed without the prior successful development of lovastatin. Thus, studying the characteristics of transformative drugs might help provide insights into how to encourage the new pharmaceutical innovation that will have the greatest effect on health outcomes.

Study Data And Methods

SURVEYS We previously surveyed expert physicians from the top thirty US academic medical centers to identify the most transformative drugs between 1984 and 2009 within fifteen medical specialties.⁴ *Drug innovation* can be defined in many ways.⁵ For the purposes of our study, a *transformative drug* was defined as one that both was innovative and had a groundbreaking effect on patient care. In two cases, a drug class as a whole was identified as being transformative in the study period, even though the first member of the class was approved by the Food and Drug Administration (FDA) before the beginning of the period (for an explanation of the methods used in selecting the study drugs, see the online Appendix).⁶

METHODS We then examined the developmental history of each drug, based on primary sources such as patents listed in the FDA's "Orange Book" and original research articles and editorials published in the peer-reviewed literature. When possible, we also interviewed key innovators who contributed to the discovery and development of a given drug. We did this to better understand the drug's origins and the pathways leading to its approval. We consulted the FDA's Orphan Drug Product designation database to determine whether the drug was designated as an orphan drug—that is, a drug intended for a rare disease (one affecting fewer than 200,000 people in the United States each year).

Using information gathered from these sources, we outlined the developmental history of each transformative drug, from basic laboratory research through preclinical and clinical testing to regulatory approval. We then analyzed patterns and themes that emerged from these data.

LIMITATIONS Several limitations to this study warrant mention. The transformative drugs were selected based on a survey of US-based experts and might not reflect the opinions of clinical experts worldwide. Since our original survey was limited to fifteen medical specialties, transformative drugs that did not clearly fit into any of these fields could have been omitted. The descriptive nature of our research made it impossible to ascribe causal relationships between the

themes of innovation and transformative drug discovery. We did not conduct a similar examination of a control group of nontransformative drugs and their developmental histories.

Additionally, our study drugs were selected as transformative based on retrospective accounts of current experts, instead of accounts at the time of the drugs' discovery. We present only brief summaries of their origins, which cannot capture the full history of these products—many of which required decades of development work. Finally, our conclusions might be affected by recall and other cognitive biases of the people who provided the historical accounts.

Study Results

Our respondents identified twenty-one drugs and five drug classes as transformative (Exhibit 1). Eighteen (69 percent) were small-molecule (chemical) drugs; the other eight (31 percent) were large-molecule (biologic) products. Four drugs were approved in 2000 or later. We found three themes in the case studies: the centrality of academic investigators and public funding in the development work, the prominence of repurposed drugs, and the large number of drugs intended for rare diseases that had a broad impact.

CENTRALITY OF ACADEMIC INVESTIGATORS

Many of the transformative drugs we identified were based on substantial drug research and development work conducted by scientists at academic medical centers, often supported by government funds including the US National Institutes of Health and similar bodies in other countries. Sometimes these academic investigators were aided by industry collaborators who provided drug samples and other technical or scientific support. In other cases, universities and academic medical centers licensed their discoveries to one or more industry partners for further development. Once clinical trials began, both industry and academic physicians or scientists were almost always closely involved.

Perhaps the most common pattern of interaction involved academic scientists' conceptualizing a therapeutic approach based on basic research about disease mechanisms and then demonstrating the proof of concept for a given molecule. Industry collaborators then developed the product for more extensive clinical testing.

Gaucher disease provides one useful case in point. This is a potentially fatal disease characterized by deficiency in the beta-glucocerebrosidase enzyme and accumulation of toxic proteins. A replacement enzyme was first harvested from human placental tissue by researchers at the NIH and the Scripps Clinic and tested in small numbers of patients in 1974, demonstrating its effi-

EXHIBIT 1

Pertinent Characteristics Of Transformative Drugs Or Drug Classes Approved By The Food And Drug Administration (FDA), 1984–2009

Drug or drug class	Discipline identifying the drug or drug class as transformative	Repurposed drug (R) ^a or orphan drug (O) ^b	Year of FDA approval ^c
ACE inhibitors	Cardiology, nephrology		1981 ^d
Alglucerase	Genetics	O	1991
Anti-VEGF agents	Ophthalmology	R	2004
Bisphosphonates	Rheumatology, endocrinology	R	1977 ^d
Clozapine	Psychiatry	R	1990
Epoetin alfa	Nephrology	O	1989
Epoprostenol	Pulmonology	O	1995
Fluoxetine	Psychiatry		1987
Fluticasone/Salmeterol	Pulmonology		2000
HIV protease inhibitors	Infectious diseases		1995
Imatinib	Oncology	O	2001
Interferon beta 1-a, 1-b	Neurology	O	1993
Latanoprost	Ophthalmology		1996
Lovastatin	Cardiology		1987
Metformin	Endocrinology	R	1994
Nitisinone	Genetics	R, O	2002
Omeprazole	Gastroenterology		1989
Onabotulinumtoxin A	Dermatology	R, O	1989
Propofol	Anesthesiology		1986
Remifentanyl	Anesthesiology		1996
Rituximab	Oncology	O	1997
Sildenafil	Urology	R	1998
Sumatriptan	Neurology		1993
Tamsulosin	Urology		1997
TNF-inhibitors	Dermatology, rheumatology	R, O	1998
Zidovudine	Infectious diseases	R, O	1987

SOURCE Authors' analysis. **NOTES** Drugs and drug classes were identified by a panel of expert physicians. Details are available in the text and the online Appendix (see Notes 4 and 6 in text). Cells with neither R nor O indicate that the drug was not initially approved as an FDA-designated orphan drug and did not fit our definition of a *repurposed drug* at the time of approval. ACE is angiotensin-converting enzyme. VEGF is vascular endothelial growth factor. TNF is tumor necrosis factor. ^aA repurposed drug is one that was originally tested for a different condition, was rediscovered after being unused or underused for a period of time, or became transformative based on use that was not for its original indication. ^bAn orphan drug is one that was approved by the FDA to treat a rare disease, typically one that affected fewer than 200,000 people per year. ^cIn the case of drug classes, the date is that of the FDA approval of the first drug in the class. ^dACE inhibitors and bisphosphonates were listed as transformative by the experts even though the first drugs in those classes were approved by the FDA before 1984.

capacity and safety.⁷ Genzyme started manufacturing the enzyme in 1981, modified it, and initiated human clinical trials of the modified enzyme in 1989. This led to the 1991 FDA approval of alglucerase (Ceredase).

A similar pattern of interaction between academia and industry contributed to the development of epoetin alfa (Epogen), the synthetic erythropoietin used to treat anemia. In that case, more than seventy years elapsed between discovery of the erythropoietin enzyme in the human body and its purification in 1971 at the University of Chicago laboratory of Eugene Goldwasser, who also reportedly proved its effect in a small,

unpublished clinical trial.⁸ With Goldwasser's help as a consultant, Amgen researchers cloned the gene that produced erythropoietin more than a decade later and produced large quantities of a biologically active product, leading to its FDA approval in 1989.⁹

The discovery of imatinib is another variation on the predominant pattern of interaction between academia and industry. The discovery of the efficacy of imatinib came from the work at the Dana-Farber Cancer Institute of Brian Druker, who set out to prove that tyrosine kinase inhibitors could inhibit the bcr-abl tyrosine kinase enzyme responsible for chronic myelogenous

leukemia (CML). NIH-funded basic research in the four decades leading up to Druker's work had identified chromosomal translocations in CML, which pointed to protein kinase overactivity. When Druker tested selections from Ciba-Geigy's library of tyrosine kinase inhibitors for activity in a laboratory model, he identified imatinib as having the greatest inhibitory action.¹⁰

Other seminal discoveries also arose first in university settings and were followed up in industry. For example, the discovery of tamsulosin (Flomax) to treat benign prostatic hypertrophy was catalyzed in 1975, when Marco Caine and colleagues at Jerusalem's Hadassah Medical Center described the alpha-adrenergic receptors in prostatic smooth muscle and reported that phenoxybenzamine, a nonselective alpha-adrenergic receptor antagonist, was effective in treating prostatic hypertrophy.¹¹ Toichi Takenaka at Yamanouchi Pharmaceuticals then showed that the alpha-1-adrenergic receptor subtype controlled prostatic smooth muscle. In collaboration with Kazuki Kawabe at the University of Tokyo, Takenaka searched for a new type of selective antagonist, which led to the discovery of tamsulosin.¹²

Academic scientists also played a central role in the discovery of the antidepressant activity of selective serotonin reuptake inhibitors (SSRIs). Their discovery dates back to the 1960s, when Arvid Carlsson and his colleagues at the University of Lund, in Sweden, investigated serotonin's role in depression. They synthesized the first SSRI, zimelidine, and showed its selective effects on serotonergic neurons in 1972 and its efficacy in treating depression shortly afterward.¹³ Also, starting in the early 1970s, a research team at Eli Lilly designed, tested, and patented fluoxetine (Prozac), which in 1987 became the first FDA-approved SSRI.¹⁴

DRUG REPURPOSING Nine of the twenty-six (35 percent) transformative products we identified were repurposed drugs originally studied for an indication different from the use for which they later became transformative, or drugs that became transformative only after a long period of limited use.

► **DRUG REDISCOVERY:** One pathway through which repurposed drugs became transformational was the rediscovery of "retired" drug compounds that had been tested and rejected by their manufacturers or clinicians for their original indications. For example, zidovudine (Retrovir) was first synthesized in 1964 by Jerome Horwitz at the Karmanos Cancer Institute in Michigan as a potential anticancer agent.¹⁵ Zidovudine was abandoned after it failed to prolong the life of animals with leukemia. Subsequently, rights to the product were acquired by Burroughs Well-

come for use in targeting the herpes virus but never survived early-stage testing.

In 1984 Samuel Broder at the National Cancer Institute solicited drug submissions from companies for antiviral candidates against HIV. He found that zidovudine's *in vitro* activity was far higher than that of any other compound provided. Clinical trials were begun promptly at NIH in collaboration with Burroughs Wellcome and clinicians at Duke University, and zidovudine was approved by the FDA as a Burroughs Wellcome product in 1987.

Metformin was rediscovered for use within its original disease class. It had existed for three decades by the 1950s, when Philippine physician Eusebio Garcia used it to treat influenza and noticed that it lowered blood sugar without any noticeable toxicity.¹⁶ French diabetologist Jean Sterne carried out preclinical studies that, by 1957, confirmed metformin's hypoglycemic effect. A related drug, phenformin, was soon marketed worldwide by Ciba-Geigy. However, it caused fatal lactic acidosis and was removed from the market, which dampened interest in metformin as well.

One of metformin's transformative turning points came in 1998, when the landmark UK Prospective Diabetes Study, a \$37 million study funded by the UK government and pharmaceutical companies, tested it in thousands of patients over an average of ten years. The study showed that metformin could control glucose and reduce the risk of myocardial infarction.¹⁶

► **DRUG REDIRECTION:** Drug repurposing also occurred via redirection toward a new indication based on new knowledge of the mechanism of a disease, a drug, or both. For example, for many years inhibitors of the cytokine tumor necrosis factor (TNF) were studied as antiseptic and anticancer agents, based on century-old observations that patients with bacterial infections sometimes demonstrated reductions in the size of cancerous tumors.¹⁷ However, recurrent testing of TNF-inhibitors to treat patients with sepsis or inhibit tumor growth showed no efficacy.¹⁸ In particular, Centocor's nebacumab (Centoxin), an anti-TNF monoclonal antibody, was approved in Europe but subsequently withdrawn after the failure of sepsis clinical trials completed to secure FDA approval.¹⁹

Meanwhile, Marc Feldmann, an immunologist at University College London, had documented expression of pro-inflammatory cytokines, including TNF, in patients with rheumatoid arthritis.²⁰ Through a personal contact at Centocor, Feldmann and his clinical partner, Ravinder Maini, received a sample of a neutralizing antibody with high affinity for TNF-alpha—which later came to be known as infliximab—to study

in twenty patients with drug-resistant rheumatoid arthritis in 1992. The patients showed immediate and lasting improvement. This success in treating an inflammatory disease led Sander van Deventer, at the Academic Medical Center in Amsterdam, to test the therapy in a child with Crohn's disease that was not responsive to any other currently available treatments.²¹

The change of fate for bisphosphonates and nitisinone was even more dramatic. Both began as nonclinical agents, but further investigation of their mechanisms of action revealed their potential for the treatment of human disease. Bisphosphonates were first synthesized in 1897. However, they were not used commercially until 1960, when they were added to detergent as complexing agents for calcium and magnesium.²²

In the early 1960s, when Proctor and Gamble sought to identify calcium-chelating agents to develop toothpaste, chemist David Francis noted that bisphosphonates reacted with calcium to form a protective barrier. He worked with Herbert Fleisch, from the Laboratory for Experimental Surgery in Davos, Switzerland, to demonstrate that bisphosphonates can counteract the biological processes that contribute to the weakening of bone seen in diseases like osteoporosis by blocking the dissolution of hydroxyapatite crystals in the bone.

On the basis of these findings, Proctor and Gamble then developed the first clinical bisphosphonate formulation, etidronate, and prepared it for clinical use. Etidronate was first used with a sixteen-month-old patient with myositis ossificans, a systemic disease of tissue calcification with a fatal prognosis, who was under the care of Andrew Bassett, an orthopedic surgeon at Columbia Presbyterian Hospital. The patient's positive response prompted researchers to investigate bisphosphonates' effects on other bone-related disorders.

In another instance of repurposing, nitisinone, originally developed as a herbicide in the 1980s, was found to cause corneal lesions in rats. Swedish researchers at Zeneca Pharmaceuticals and Gothenburg University discovered that this effect was caused by inhibiting 4-hydroxyphenylpyruvate dioxygenase, a liver enzyme involved in metabolizing excess tyrosine that is also the enzyme responsible for the disease manifestations of hereditary tyrosinemia type 1. The agent was given to five patients in Sweden with dramatic clinical effect.²³

► **OFF-LABEL AND SECONDARY USE:** A third pathway for repurposed drugs was the discovery of unintended favorable secondary effects during original drug testing or use. For example, the study of vascular endothelial growth factor (VEGF) began with the work of Judah Folkman

at Harvard Medical School. In 1971 Folkman developed the hypothesis that "angiogenesis factors" were secreted by tumors that encouraged the growth of vasculature to supply it. During the ensuing decades, with US government and pharmaceutical company support, he tested numerous compounds for their anti-angiogenesis properties, hoping to find an anticancer agent.

Based on this work, VEGF was isolated and cloned in 1989 by Napoleone Ferrara at Genentech, which then developed anti-VEGF antibodies to test as anticancer agents. This led to the development of bevacizumab (Avastin), which was originally indicated for colorectal cancer and has earned Genentech over \$30 billion since its 2004 approval. Meanwhile, researchers in Folkman's laboratory, as well as others at the Massachusetts Eye and Ear Infirmary and Joslin Diabetes Center, showed that VEGF was also a major cause of vascular leakage and angiogenesis in the eye—which led to age-related macular degeneration (AMD)—and that blocking VEGF could inhibit this pathological process. As a result, bevacizumab (Avastin) began to be used off-label for AMD, and angiogenesis inhibitors became a transformative drug class for this cause of blindness. The FDA approved a derivative of bevacizumab, ranibizumab (Lucentis), for use in AMD in 2006.²⁴

Sildenafil and onabotulinumtoxin A became transformative medications because of unexpected side effects. Sildenafil (Viagra), synthesized in 1989 by Pfizer scientists, began as a candidate for treating angina. It was a potent inhibitor of phosphodiesterase type 5, an enzyme involved in smooth muscle relaxation. In early clinical studies, sildenafil's short half-life and drug-drug interactions limited its prospects as an anti-anginal product, but erections were a common side effect reported by male study patients. This, in conjunction with a new understanding in the early 1990s of the mechanism of smooth muscle function in the penis, caused Pfizer to change sildenafil's fate.²⁵

Onabotulinumtoxin A (Botox), a neurotoxin derived from the bacterium *Clostridium botulinum* that creates long-lasting paralysis, had a similarly unexpected fate. The bacterium was first isolated in 1895, and its toxins were used for biological warfare throughout World Wars I and II. In 1979 Edward Schantz, a biochemist at the University of Wisconsin, developed a method of producing large batches of the toxin in a crystallized form, which was later approved for use in humans by the FDA for the treatment of conditions of hyperactive extraocular muscles. In 1987 Jean Carruthers, a Canadian ophthalmologist who treated patients for blepharospasm (uncontrollable closure of the eyelids), noted that the

toxin had an interesting secondary effect: Her patients' frown lines disappeared. Her observation became the basis for the drug's transformative role in cosmetic dermatology.²⁶

ORPHAN DRUGS Ten of the twenty-six (38 percent) transformative drugs or drug classes in our sample had been initially approved by the FDA as orphan drugs. Zidovudine, for example, met the criteria for orphan classification because of the limited known scope of the HIV epidemic at the time of its approval.

Other orphan drugs became transformative not only for patients suffering from rare diseases, but also because they opened up new therapeutic pathways or established a new understanding of disease. Imatinib (Gleevec) was revolutionary for proving that it was possible to inhibit tyrosine kinases, which helped advance the era of targeted cancer therapy. Similarly, alglucerase's impact on Gaucher disease helped encourage the development of replacement therapies for other diseases caused by enzyme deficiencies.

Finally, orphan drugs such as rituximab and infliximab were transformative both because they helped confirm the therapeutic potential of antibody-based therapy and because they ended up addressing mechanisms of disease—B cell-mediated disease and inflammation, respectively—and thus became useful in treating a variety of conditions.

Discussion

The transformative drugs in our sample were discovered at different institutions at various times during the twenty-five-year study period, and they represent a range of molecular structures. Yet we found three common themes that often predicted successful drug innovation. First, many of the key insights behind these transformative products emerged in publicly funded basic research in university settings and were then further developed through collaboration between public and private entities. Second, a substantial number of the drugs became significant after being repurposed from targeting a different indication. Third, a high proportion were designed to treat rare diseases but became transformative by opening up new therapeutic pathways or establishing a new understanding of pathology.

Our review of transformative medications revealed the crucial initial role played by innovative individual scientists, often based in academic medical settings but some based in industry laboratories. Despite the widespread perception that major drug discoveries come primarily from the pharmaceutical industry, our review indi-

cates that for most transformative drugs, the story is more complex.

These findings do not negate the often vital role played by drug companies in the development of new drugs. Collaborations occurred between industry scientists and academic researchers and moved a seminal discovery into product development. In a few instances, the pivotal insights that led to the creation of a transformative product did arise wholly within the research enterprise of a single company. But our findings do not support the concept of the pharmaceutical industry as the single most important source of transformative drug development.

Correctly identifying the sources of transformative drug products can have important implications for policy making. The centrality of academic centers and public funding in pharmaceutical development has been noted in other studies.²⁷ However, it is frequently challenged by those who argue that research within companies is the main source of innovative drug products.^{3,28,29} This claim has been used to justify high prescription drug prices, especially in the United States, to support the continuing supply of innovative products.

Companies clearly play a major role in funding and conducting the clinical trials necessary to gain FDA approval. However, the fraction of pharmaceutical sales revenue devoted to total research and development is generally under 20 percent.³⁰ Furthermore, the share spent on the basic research that often generates truly innovative new compounds is estimated to be far smaller.³¹ Thus, it is not surprising that the insights underlying the creation and transformative effect of certain drugs, such as the concepts that TNF blockers can curb inflammatory diseases and that blocking angiogenesis can kill tumors and treat macular degeneration, arose primarily in academic or government-sponsored settings.

However, the insights themselves are not patentable, because ownership under patent law is generally reserved for specific products, methods, and processes. The commercial development of products based on these insights, and the ownership of the resulting intellectual property, therefore, often occurs within a pharmaceutical company, leading to subsequent misperceptions about the origins of these products. For a few drugs in our sample, the academic scientists both sufficiently developed the drugs to patentable stages and sought patents through their academic medical centers, resulting in financial returns, as in the case of infliximab and New York University. This model has become increasingly common, but its implications on transformative drug innovation are unknown.

Proposals to promote drug innovation often focus on providing greater incentives for drug manufacturers by extending patent terms or reducing regulatory barriers to FDA approval, instead of focusing on increasing support for the research that is so often the source of innovative therapeutic ideas. In fact, reductions in NIH funding and in industry support for its own laboratories in recent years have threatened the funding streams that we found supported most transformative drug innovation. Venture capital funds supporting early-stage research have also become more limited because such work often does not yield immediately patentable products.

Policies that support biomedical research and those that foster the development of ideas, such as open-source drug development, may be more powerful ways of producing more transformative drugs in the future. For example, the World Intellectual Property Organization's Re:Search program fosters the sharing of intellectual property and resources among its public and private partners to target nineteen neglected tropical diseases, malaria, and tuberculosis, with the goal of overcoming the lack of economic incentives for companies to pursue these areas independently.³² Other solutions that have been proposed include public-private partnerships, such as the NIH's Accelerating Medicines Partnership, an effort to bring experts from companies and academia together to identify biomarkers that might be applied to future drug candidates, with the results ultimately made public "similar to the open-source movement in computing."³³

The successful repurposing of many of the drugs in our sample suggests that this pathway is a means of creating breakthrough innovations. The New Therapeutic Uses program at the NIH's National Center for Advancing Translational Sciences represents one current attempt to purposefully repurpose stalled investigational drugs. Going forward, such reuse may be limited by pharmaceutical companies' retention of proprietary rights, even with respect to compounds not being pursued because of business or other nonclinical considerations.³⁴ Given the potential this creates for missed therapeutic opportunities, the New Therapeutic Uses program has identified twenty-six compounds that had undergone significant development, including human safety testing, and made them available to interested academic researchers.³⁵

The success of drugs for rare diseases in broadly transforming clinical care shines a bright light

on the Orphan Drug Act of 1983, which was designed to stimulate the development of drugs for rare diseases by offering manufacturers financial incentives such as tax breaks, waived regulatory fees, and guaranteed periods of market exclusivity.³⁶ The manufacturers of orphan drugs also benefit from several other advantages in the regulatory approval process.

For example, the FDA is traditionally more lenient with orphan drugs in terms of the size and organization of premarket clinical trials. Such drugs can be approved on the basis of uncontrolled and unblinded studies that use small numbers of patients and that are more likely to test surrogate clinical outcomes (such as tumor size or biomarker change) than traditional clinical outcomes such as mortality or symptom relief.³⁷

Paradigm-changing drugs like imatinib or zidovudine likely benefited from being tested in smaller populations of patients who had no other reasonable alternative. By contrast, a drug with a new mechanistic approach to treating diabetes would need to be tested in larger, more demanding trials, which might be perceived as financially riskier for manufacturers. Greater investment in research on treatments for rare diseases could help uncover more transformative drugs; this also suggests the potential utility of nonconventional trial designs in speeding the drug evaluation process, as long as they do not sacrifice rigor for speed. Additional studies can help determine whether transformative orphan drugs are different from other orphan drugs that have only a modest impact on patient outcomes or are later found to be unsafe and removed from the market.

Conclusion

This analysis of the most transformative drugs of the past twenty-five years indicates that such products often emerge as a result of processes that current policy makers and business leaders undervalue, including government investment in academic-based science and the repurposing of older products that have failed in early testing and may be nearing the end of their patent-protected exclusivity periods. Further assessment of the origins of transformative drugs such as these is likely to yield additional insights into which scientific and policy strategies will be most likely to encourage the development of equally important new medications in the future. ■

This research was previously presented at the annual meeting of the Robert Wood Johnson Investigator Award in Health Policy Research, Indianapolis, Indiana, September 17–19, 2014. The

research was funded by a grant from the Robert Wood Johnson Investigator Award in Health Policy Research program. Aaron Kesselheim is also funded by the Greenwall Faculty Scholar

program and the Harvard Program in Therapeutic Science. The authors thank Lara Maggs for her helpful comments on a previous version of the article.

NOTES

- 1 Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov.* 2011;10(6):428–38.
- 2 Arrowsmith J. A decade of change. *Nat Rev Drug Discov.* 2012;11(1):17–8.
- 3 Lincker H, Ziogas C, Carr M, Porta N, Eichler HG. Regulatory watch: where do new medicines originate from in the EU? *Nat Rev Drug Discov.* 2014;13(2):92–3.
- 4 Kesselheim AS, Avorn J. The most transformative drugs of the past 25 years: a survey of physicians. *Nat Rev Drug Discov.* 2013;12(6):425–31.
- 5 Kesselheim AS, Wang B, Avorn J. Defining “innovativeness” in drug development: a systematic review. *Clin Pharmacol Ther.* 2013;94(3):336–48.
- 6 To access the Appendix, click on the Appendix link in the box to the right of the article online.
- 7 Garber AM, Clarke AE, Goldman DP, Gluck ME. Federal and private roles in the development and provision of alglucerase therapy for Gaucher disease [Internet]. Washington (DC): Office of Technology Assessment; 1992 Oct [cited 2014 Dec 5]. Available from: <https://www.princeton.edu/~ota/disk1/1992/9214/9214.PDF>
- 8 Easton J. Eugene Goldwasser, biochemist behind blockbuster anemia drug, 1922–2010. *UChicagoNews* [serial on the Internet]. 2010 Dec 22 [cited 2014 Dec 8]. Available from: <http://news.uchicago.edu/article/2010/12/22/eugene-goldwasser-biochemist-behind-blockbuster-anemia-drug-1922-2010>
- 9 Lin FK, Suggs S, Lin CH, Browne JK, Smalling R, Egrie JC, et al. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A.* 1985;82(22):7580–4.
- 10 Frances MD, Valent DJ. Historical perspectives on the clinical development of bisphosphonates in the treatment of bone diseases. *J Musculoskelet Neuronal Interact.* 2007;7(1):2–8.
- 11 Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule, and bladder neck. *Br J Urol.* 1975;47(2):193–202.
- 12 Takenaka T. Legends in urology. *Can J Urol.* 2010;17(5):5344–5.
- 13 Carlsson A. A historical note on the development of zimelidine, the first selective serotonin reuptake inhibitor. *Eur Psychiatry.* 1996;11(Suppl 4):S235–6.
- 14 Wong DT, Perry KW, Bymaster FP. Case history: the discovery of fluoxetine hydrochloride (Prozac). *Nat Rev Drug Discov.* 2005;4(9):764–74.
- 15 Nussbaum B. Good intentions: how big business and the medical establishment are corrupting the fight against AIDS. New York (NY): Atlantic Monthly Press; 1990.
- 16 Dronsfield A, Ellis P. Drug discovery: metformin and the control of diabetes. *Education in Chemistry.* 2011; Nov:185–7.
- 17 Mueller H. Tumor necrosis factor as an antineoplastic agent: pitfalls and promises. *Cell Mol Life Sci.* 1998;54(12):1291–8.
- 18 Qiu P, Cui X, Barochia A, Li Y, Natanson C, Eichacker PQ. The evolving experience with therapeutic TNF inhibition in sepsis: considering the potential influence of risk of death. *Expert Opin Investig Drugs.* 2011;20(11):1555–64.
- 19 Schoemaker HJ, Schoemaker AF. The three pillars of bioentrepreneurship. *Nat Biotech.* 1998;16(Suppl):13–5.
- 20 Feldmann M, Maini R. Discovery of TNF-alpha as a therapeutic target in rheumatoid arthritis: preclinical and clinical studies. *Joint Bone Spine.* 2002;69(1):12–8.
- 21 Van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, Jansen J, Tytgat GN, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology.* 1995;109(1):129–35.
- 22 Francis MD, Valent DH. Historical perspectives on the clinical development of bisphosphonates in the treatment of bone diseases. *J Musculoskelet Neuronal Interact.* 2007;7(1):2–8.
- 23 McKiernan PJ. Nitisinone in the treatment of hereditary tyrosinaemia type I. *Drugs.* 2006;66(6):743–50.
- 24 Kim LA, D'Amore PA. A brief history of anti-VEGF for the treatment of ocular angiogenesis. *Am J Pathol.* 2012;181(2):376–9.
- 25 Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov.* 2006;5(8):689–92.
- 26 Ting PT, Freiman A. The story of Clostridium botulinum: from food poisoning to Botox. *Clin Med.* 2004;4(3):258–61.
- 27 Stevens AJ, Jensen JJ, Wyller K, Kilgore PC, Chatterjee S, Rohrbaugh ML. The role of public-sector research in the discovery of drugs and vaccines. *N Engl J Med.* 2011;364(6):535–41.
- 28 Reichert JM, Milne CP. Public and private sector contributions to the discovery and development of “impact” drugs. *Am J Ther.* 2002;9(6):543–55.
- 29 Holmer AF. Testimony by President and CEO of PhRMA before the Senate Committee on Health, Education, Labor, and Pensions. Congressional Record, S. Hrg. 106-651 (13 June 2000) [Internet]. Washington (DC): Government Printing Office; 2000 [cited 2015 Jan 2]. p. 91. Available from: <https://ia601407.us.archive.org/12/items/drugsafetypricin00unit/drugsafetypricin00unit.pdf>
- 30 Pharmaceutical Research and Manufacturers of America. 2013 profile: biopharmaceutical research industry [Internet]. Washington (DC): PhRMA; 2013 Jul [cited 2014 Dec 8]. Available from: <http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf>
- 31 Light DW, Lexchin J. Foreign free riders and the high price of US medicines. *BMJ.* 2005;331(7522):958–60.
- 32 Ramamoorthi R, Graef KM, Krattiger A, Dent JC. WIPO Re: Search: catalyzing collaborations to accelerate product development for diseases of poverty. *Chem Rev.* 2014 Sep 17. [Epub ahead of print].
- 33 Editorial Board. NIH tries a new approach to speed drug development. *Washington Post.* 2014 Feb 8.
- 34 Allison M. NCATS launches drug repurposing program. *Nat Biotechnol.* 2012;30(7):571–2.
- 35 National Center for Advancing Translational Sciences. Discovering new therapeutic uses for existing molecules [Internet]. Bethesda (MD): NCATS; 2014 May [cited 2014 Dec 8]. Available from: <http://www.ncats.nih.gov/files/factsheet-therapeutics-rev.pdf>
- 36 Braun M, Frag-El-Massah S, Xu K, Cote T. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat Rev Drug Discov.* 2010;9(7):519–22.
- 37 Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs non-orphan drugs for cancer. *JAMA.* 2011;305(22):2320–6.