Financing Drug Innovation in the US: Current Framework and Emerging Challenges

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Abstract

The current US drug innovation financing framework rests on the notion that a defined period of marketing exclusivity combined with the expectation of reimbursement for clinically valuable, cost-effective therapies, followed by vigorous price competition from generic drugs and biosimilars ensures a sufficient return on investment (ROI) to incent private sector risk-based investment and research and development activities while providing access for new treatments to patients. While periodically, alternatives such as government prizes, direct purchases or development, and limits on certain incentives have been proposed, the basic approach has remained intact since the 1980s, with incremental provisions addressing specific gaps and priorities, and adding provisions for biosimilar entry. This paper reviews the main elements of the current US system to financing drug innovation and its approach to balancing multiple objectives. In addition, the system for financing drug innovation must be effective over a wide range of potential scientific approaches and economic conditions. It should be predictable for investors and payers making long-term development and coverage decisions, while also encompassing unanticipated new treatment modalities and scientific progress. An important emerging challenge is posed by clinically transformative, high-investment, single-administration therapies, such as gene therapy. Continued experimentation and the input of a range of stakeholders are needed to ensure next-generation therapeutic advances continue to be developed and made available to patients.

1 Introduction

Biopharmaceutical innovation has contributed to important public health improvements over the past century. Many previously fatal diseases, from HIV and hepatitis C to various cancers, now can be managed as chronic conditions, leading to improvements in mortality and morbidity [1, 2]. Other diseases have been prevented, as reflected in the declining rate of hospitalization for heart disease over time [3]. Moreover, we have entered an age of promising, next-generation scientific approaches to diseases that previously had limited or no effective treatment: three gene therapies are Food and Drug Administration (FDA)

Key Points for Decision Makers

Systems to finance drug innovation must balance multiple objectives, providing effective incentives to develop valuable new therapies, encouraging competition to drive down prices, and limiting what people have to pay when sick so that everyone can afford necessary care.

In addition, they should provide predictable frameworks to payers and innovators making long-term investment and coverage decisions, while accommodating unanticipated scientific advances.

The absence of a sustainable insurance coverage and payment model could challenge patient access to new breakthrough therapies like gene therapy, and undermine incentives for their future development.

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approved; nearly 300 gene therapies, gene-modified cell therapies, genome editing therapies, or oncolytic viruses are in clinical development; and 425 active gene therapy studies are listed with ClinicalTrials.gov [4, 5]. In 2018,

the FDA reported more than 500 active investigational new drug applications involving gene therapy products, and it predicts that by 2025, it will be approving 10–20 cell and gene therapy products a year [6–8].

In order to realize the potential of diverse new disease approaches, the system for financing drug innovation must be effective over a wide range of potential scientific approaches and economic conditions. An ideal financing system for pharmaceuticals balances multiple objectives: it provides incentives to develop valuable new therapies; it encourages competition to drive down prices; and it limits what people have to pay when sick so that everyone can afford necessary care. The first two goals represent a tradeoff between providing effective incentives for the development of innovative new treatments and promoting competition and maximizing patient access through lower prices. The third is associated with the completeness of insurance, what services are covered, and how much is paid by the insurer relative to the insured.

While the challenge of insurance coverage for a new higher-priced treatment is not a new one, the scale of the challenge may increase many-fold due to the characteristics of these new therapies. The list price at launch for the first approved chimeric antigen receptor T cell (CAR-T cell) therapy was US\$475,000 per patient (associated costs of therapy delivery and follow-up in cancer centers increases the total cost to in excess of US\$1 million, according to informal estimates by a recent panel [9]), and future “once-and-done” gene therapies might cost multiple millions per person treated, all costs included [10]. While it is hard to predict the number of new therapies that will be approved and the number of patients treated, one estimate speculates that in 2030, perhaps 50,000 US patients might be treated with cell and gene therapies, with the majority in cancer [11]. At a hypothetical cost of US\$1 million per patient, annual outlays then would reach US\$50 billion (as a comparison, total net spending on prescription drugs in the US was estimated to be US\$344 billion in 2018 [12]). Some would be launched in indications where they would displace a less-effective but also quite expensive, often chronic, current standard of care, and therefore the incremental cost to the system would be substantially less than this figure. Nevertheless, even highly cost-effective, curative therapies might pose a substantial upfront budget impact and affordability challenges for some payers.

The absence of a sustainable insurance coverage and payment model could limit patient access to new breakthrough therapies and undermine incentives for their future development. Conversely, reducing reimbursement risk by clarifying new payment and reimbursement models could encourage additional investment and provide clarity to patients and their families. The system of financing pharmaceutical innovation

should be predictable for investors and payers making long-term development and coverage decisions, while also encompassing unanticipated new treatment modalities and scientific progress.

The current US framework has been in place with some modifications since the early 1980s, with the passage of the Hatch–Waxman Drug Price Competition and Patent Term Restoration Act of 1984 (informally, “Hatch–Waxman”) [13] enabling streamlined generic drug entry, the Bayh–Dole Drug Price Competition and Patent Term Restoration Act of 1980 [14] and the Stevenson–Wydler Technology Innovation Act of 1980 [15] encouraging technology transfer from universities and federal labs, respectively, and the development of the modern biopharmaceutical risk-based investment ecosystem. While research and development (R&D) investment decisions are global in nature and the US framework of law, regulation, and economic incentives is by no means the only consideration, given the US’s position as the world’s largest biopharmaceutical market, it is undoubtedly an important one.

In this article, we provide a high-level overview of the US approach to financing drug innovation, and identify various proposals to change it, in the context of the goals of providing incentives for innovation, promoting competition, and ensuring access. Finally, we briefly consider whether the entry of high-priced, potentially curative gene therapies over the next decade will be challenged by, and challenge, the current approach.

2 Context: The Drug Development Economic Challenge

The process of developing, approving, and commercializing a new drug is a lengthy, costly, and risky one [16]. According to the most recent analysis in a series, the R&D process averages more than 10 years from synthesis to approval, with average direct costs per approved new compound of US\$1.4 billion (in 2013 dollars) when the cost of failed attempts are included (when fully capitalized to the time of launch at a discount rate of 10.5%, the total is US\$2.6 billion) [17]. Regardless of the specific figures, because historically, fewer than one in eight drug candidates entering phase I clinical testing result in an approval and revenues from new drugs are highly skewed, the few approved drugs which are commercially successful fund R&D costs for the development portfolio [18–21].

Against this backdrop, since the 1980s, a complex ecosystem supporting biopharmaceutical innovation has developed, connecting university researchers, spin-off and start-up firms, and sources of risk-based investment capital [22]. To attract investment capital, these start-up firms rely on the likelihood their candidate drugs will address valuable unmet medical needs when and if they are eventually approved, the

strength of intellectual property (IP) protection, and expectations regarding reimbursement and payment if they are approved. Without IP protections and favorable expectations regarding eventual reimbursement and payment for clinically valuable drugs, firms would be unlikely to make the substantial, risky investments needed to develop them, or to acquire early-stage discovery firms or their assets. With some two-thirds of 2018 new active substance (NAS) launches originated by emerging biopharmaceutical companies (those with sales less than US\$500 million or R&D spending less than US\$200 million), incentives and expectations in early-stage development are critical elements in the innovation system [23].

3 The Current Framework of Investment Incentives

A foundational assumption of the existing US innovation financing framework is that an exclusivity period, combined with the expectation of reimbursement for clinically valuable, cost-effective therapies, ensures a sufficient return on investment (ROI) to incent private sector risk-based investment and R&D activities.

The core framework for the current system of drug innovation financing in the US is the *Hatch–Waxman Act*. In *Hatch–Waxman*, Congress struck a balance between strengthening incentives for innovators, thereby ensuring the next generation of drug treatment, and reaping costs savings from price competition after generic entry.

On the one hand, *Hatch–Waxman* created a new, lower-cost abbreviated new drug application (ANDA) route to market for generic drugs, under which manufacturers could demonstrate bioequivalence to an innovative reference product already approved. Further incentives were provided to spur generic drug entry, by making the first company to file an ANDA with a patent challenge eligible for 180 days of generic drug market exclusivity when it is the only generic drug competitor on the market and therefore can earn higher profits during this period of time.

Over time, patent challenges have become more common and have occurred sooner after the originator product's launch date. Specifically, approximately three in four new small-molecule drugs with first generic entry in 2014 (and more than nine in ten with substantial sales in the preceding year) faced patent challenges by potential generic competitors, up from less than one in ten in 1995 [24]. At the same time, the Federal Trade Commission (FTC) has expressed concerns about certain patent settlement agreements between branded and generic manufacturers with the potential to delay generic entry (so-called “pay-for-delay” settlements).

On the other hand, for innovators, in recognition of the lengthy process of clinical testing and regulatory review, which eats away at the available period of patent protection, *Hatch–Waxman* includes partial patent term restoration for new molecular entities (capped at 5 years, with the extended patent term no longer than 14 years from FDA approval). It also includes 5 years of exclusivity for new molecular entities (that runs concurrently with patent term protection).

Over time, Congress has supplemented these provisions by enacting special exclusivity incentives and other incentives (such as tax credits) that supplement baseline patent and exclusivity period provisions to address areas of perceived under-investment, including clinical studies in pediatric populations and studies of “orphan” drugs (to treat rare diseases affecting fewer than 200,000 people in the US each year). Other special incentives encourage investment in neglected tropical and rare pediatric diseases, and antibiotic development [16].

In this way, the *Hatch–Waxman* framework and the current system that has grown up around it relies on defined periods of marketing exclusivity, followed by incentives for generic drug entry and aggressive price competition. Potential threats to generic drug entry and price competition, whether through collusion, efforts to maximize generic prices by preventing additional generic entrants, or incentives to extend exclusivity periods unduly without countervailing brand-to-brand competitive pressure, could impact its continued effectiveness, and therefore are scrutinized closely by government.

The resulting industry-wide average market exclusivity period (including the effects of any special exclusivity incentives that may apply), defined as the period of time between first branded sale and first generic sale, has changed relatively little over the past 20 years, varying only between a low of 12.2 (2007–2008) and a high of 13.7 years (1997–1998) (figures are for 2-year cohorts of drugs experiencing first generic drug entry between 1995–1996 and 2013–2014) [24].

A comparable framework for biologics had lagged in the US; through the *Biologics Price Competition and Innovation Act* of 2009 (BPCIA, part of the *Patient Protection and Affordable Care Act*), Congress provided corresponding, though not identical, incentives for competitive developments in the biologics and biosimilars market [25]. Under the BPCIA, new biologics receive 12 years of legislative exclusivity (patent protection runs concurrently, providing varying lengths of protection, higher or lower). The BPCIA also created a regulatory pathway for biosimilars that can demonstrate no clinically meaningful differences in safety and efficacy relative to a reference biologic [the so-called 351(k) pathway] [26]. For a biosimilar to be approved as interchangeable with its reference product, a higher standard, the manufacturer must demonstrate that it would be expected

to produce the same clinical result as the reference product in any given patient [27]. The BPCIA also defined a framework for patent challenges [28].

A number of biosimilars have been approved in Europe, beginning in 2006 [29]. However, biosimilar competition in the US has lagged. The first biosimilar product (filgrastim-sndz) was only launched in the US in September 2015 [30]. As of December 2019, the FDA had approved 26 biosimilar applications under the new 351(k) pathway, of which approximately half have launched in the US (all were approved as being biosimilar to, but not interchangeable with, their reference products) [31]. The ultimate impact of the new framework and the entry of biosimilars on the US market for biologic drugs is not yet known.

4 Alternative Drug Innovation Financing System Proposals: Grants, Contracts, Prizes, and Limits

Periodically, alternative approaches have been suggested that would alter the current drug innovation financing structure and address one or more of the goals identified earlier. Some focus on the first element (innovation incentives), by altering the mix or value of the current patent and legislative exclusivity-based incentives. For example, some proposals would add new, targeted incentives (e.g., additional periods of exclusivity for certain types of drugs or diseases), restrict the value of others (e.g., by reducing the length of exclusivity periods or “clawing back” the value of orphan drug incentives for some commercially successful drugs), or supplement the current system with government prizes or other targeted activity such as direct government contracting or drug development to address areas of public health priority but market failure (e.g., for new antibiotics) [32].

Others focus on the second element (competition), by ensuring adequate generic competition (e.g., by eliminating barriers to prompt generic drug entry [33], or “pay-for-delay” settlements, or abuse of the patent system). Quantifying the relative impacts can be difficult, however, not least because of the difficulty of assessing the uncertain effects of future benefits foregone (in this case, new therapies that are not developed that otherwise might have been). The Congressional Budget Office (CBO) reflected the importance of attempting to do so, however, in its recent estimate of the impact of proposed legislation to change various aspects of the Medicare drug program, by including a section on “Effect on Pharmaceutical Research and Development” in addition to its estimate of the direct impact of the proposals on the federal budget [34].

Some critics of the current innovation financing system that relies on these exclusivity-based incentives for private

investment have advocated replacing or supplementing it with a system of prizes, direct government contracting, direct government R&D activity, or other options [35]. Under a prize system, the government would specify a particular product or outcome (e.g., a highly effective hepatitis C drug) and a reward to the first manufacturer to meet the defined clinical or other parameters; prizes are generally “winner takes all.” Under a system of government contracting, the government would issue a request for bids for the specified product or outcome, and would award one or more contracts; “advanced market commitments” (AMCs) or purchase volumes promised in advance could be specified in the contract. Under direct government R&D activity, the government itself would conduct drug development activities, for example, in areas of public health priority but potential private market failure (e.g., antibiotics) [32]. Under each type of system, additional government spending would be required, which would be funded through additional federal taxes, potentially offset over time by lower prices for the drugs covered by these programs than would otherwise have been the case (when the specific contract terms are fulfilled or the prize is awarded). One advantage of some prizes and contracts is that they can be structured to result in lower pharmaceutical prices at the time when people receive care, thereby reducing patient access barriers to necessary care. For example, a drug whose patent owner had agreed to an upfront payment or prize in exchange for such lower prices (or an outright sale of patent rights to the government) could be sold at the lower marginal cost of production. One argument made for prizes relative to contracts is that by rewarding only successful outcomes, they focus on outputs rather than inputs [16].

But there are drawbacks as well. Others have discussed the challenges associated with these proposals, particularly in the context of whether they would be mandatory alternatives or voluntary supplements to the existing system [16]. Theoretically, mandatory alternatives could achieve more immediate generic price competition and lower prices, but might also introduce concerns that innovation incentives would be reduced and therefore that fewer new therapies would be developed over time. Another practical concern raised relates to the level of additional federal spending implied—fully replacing the current system of private investment would result in taxpayer commitment to additional federal outlays of tens of billions of dollars each year without immediate cost savings [36].

In addition, others have suggested relying solely on government grants and contracts would “require a degree of centralized information and decision making that would likely be incompatible with the current dynamic, risk-based investment and business environment.” [16] Prizes often are structured as “winner-takes-all” competitions, whereas clinical advances may result from a series of incremental

improvements, and competition in a given therapeutic category can yield rapid changes, as was the case recently with competing new hepatitis C therapies.

Substituting direct government activity for private sector investment on a mass scale from early-stage discovery to launch and post-launch activities would require the development of substantial later-stage R&D and commercial expertise among federal agencies. In comparison, under the current system, technology transfer under the *Bayh-Dole Act* and *Stevenson-Wydler Act* from universities and federal laboratories, respectively, to private sector partners for further development and commercialization is thought to reflect complementary roles for the public and private sectors, with National Institutes of Health (NIH)-funded intramural research and extramural grants typically supporting earlier R&D activities.

AMCs, or enforceable promised future purchases, have been discussed as one mechanism to encourage investment in lower monetary value disease markets (such as malaria), whether the incentive is a prize or a contract. A creative example is Louisiana's competitive bid process for a partner to provide unlimited hepatitis C drug access to its Medicaid and prison population for a period of 5 years. Under the subscription model agreement, the state will treat as many as it can for a fixed amount, versus paying per treatment [37]. Globally, the AMC approach was applied to pneumococcal vaccines in a pilot project launched in 2009 [38], and has been proposed as one potential mechanism for COVID-19 vaccine development financing [39, 40].

Using prizes as targeted voluntary supplements to patents addresses concerns about undermining investors' expectations of future rewards [41]. Such an approach has been used in the case of the Priority Review Voucher program, which rewards successful investments in neglected tropical and rare pediatric diseases and biologic, chemical, radiologic, or nuclear threat medical countermeasures with vouchers which can be sold to other manufacturers and used for a Priority Review for another drug not otherwise eligible for one.

Others have proposed retaining the current private investment incentive-based system but using increased government regulation to limit the value of certain current incentives. Such proposals have taken the form of, for example, allowing for "clawback" of the value of incentives if drugs "earn enough to suggest, ex post, that they could have been developed without such incentives" (e.g., orphan drugs with sales exceeding a certain level) [42]. The long-term effects of approaches which aim to adjust the relative balance between providing incentives for future innovation and reducing prices, thereby increasing patient access to current drugs, is unknown, as regulation that curtails the upper tail of the potential payoff to innovators could affect incentives for future innovation to some degree, depending on the specifics.

5 An Emerging Challenge: Sustainable Innovation Financing Models for Certain Curative Therapies

As noted, the existing innovation financing framework rests on the assumption that an exclusivity period, combined with the expectation of reimbursement for clinically valuable, cost-effective therapies, ensures a sufficient ROI to incentivize private sector R&D risk-based investment. However, if an emerging therapy area faces substantial questions about reimbursement, the uncertainty may limit investment.

This concern has been raised in the context of certain emerging clinically transformative, high-investment curative therapies such as gene therapy [43]. These high-investment technologies face intense payer scrutiny due to their single-administration and associated high upfront "sticker price," exacerbated by the potential for patient switching from one payer to another over time (so that the payer covering the therapy and making the upfront payment may not be the same payer that experiences the future stream of medical care offsets). As noted, even when shown to be cost-effective, potential upfront budgetary impact payer concerns could undermine patient access and the diffusion of clinical benefits from the new therapies.

Recent research by some of us has found that payers have high levels of concern about the financial risk and potential impact of gene therapies, and would consider alternative payment models, under the right circumstances [44]. Alternatives to a single upfront payment for the gene therapy could include breaking it up into multiple payments tied to pre-defined clinical milestones and smoothing the payment into a stream of payments over multiple years (so-called "drug mortgages" or pay-over-time schemes). However, given uncertainty about the magnitude and duration of the clinical effects of the new therapies, payers likely would require performance guarantees as part of the payment model. In addition, many payers are uncomfortable with "patient portability" features, where a multi-year agreement includes an obligation to continue payments for the therapy over time, regardless of whether the patient remains with the original insurer or switches to another. In a new era of high-investment, potentially curative therapies where a "once-and-done" intervention may create a lifetime of health, effective payer reimbursement models will be critical aspects of the innovative financing model, and multiple creative approaches may emerge from experimentation. A number of commentators have noted that government can play a key role in removing impediments to such experimentation, such as addressing price reporting and related regulatory obstacles with appropriate steps [45].

6 Conclusions and Observations

The existing US framework under *Hatch–Waxman*, the *BPCIA* and subsequent targeted incentives aim to balance incentives for continued innovation with competitive market entry and affordable access to treatment. Put differently, it aims to strike an appropriate intergenerational balance between ensuring access to treatments that currently exist with incentives for access to those that do not yet exist, and relies on a set of incentives for private sector risk-based investment to do so.

There have been periodic suggestions for alternative approaches to replace, extend, or curtail its provisions, ranging from direct government contracting, a greater government direct role in R&D, to incremental regulation meant to address specific market failure gaps or to limit the maximum economic rewards to certain innovation investments. In assessing various proposals related to financing innovation, policy-makers should consider their effect on the balance among the goals of encouraging continued investment in tomorrow's novel drug therapies, safeguarding competition, and ensuring patient financial access. Due to the important role the US plays in the biopharmaceutical market, substantial changes to the current framework have the potential for far-reaching implications for patients both in the US and around the world.

Looking ahead, an important emerging issue is the coverage and payment model challenges associated with clinically transformative, high-investment, single-administration therapies, such as gene therapy. The current model for financing drug innovation, which relies on the promise of future returns to incent private investment, has been associated with advances in many disease areas, therapeutic modalities, and new scientific approaches, while gaps remain in some important areas such as antibiotics. In order to sustain incentives for future development of such treatments and other novel clinical modalities, manufacturers and payers are investigating a range of innovative financing models that will allow sufficient returns for innovators while ensuring access for future patients. Continued experimentation and the input of a range of stakeholders are needed to ensure next-generation therapeutic advances continue to be developed and made available to patients.

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Compliance with Ethical Standards

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References

1. Cutler D, Deaton A, Lleras-Muney A. The determinants of mortality. *J Econ Perspect*. 2006;20(3):97–120.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30.
3. Cutler D, Ghosh K, Messer K, et al. Explaining the slowdown in medical spending growth among the elderly, 1999–2012. *Health Aff (Millwood)*. 2019;38(2):222–9.
4. EvaluatePharma, a proprietary database, listed 289 such therapies in clinical development, as of November 6, 2019, and estimated that more than 30 new gene therapies will be approved by the FDA over the next decade, taking into account potential failures in development. <https://www.evaluate.com/>. Accessed 6 Nov 2019.
5. Defined as those that match “gene therapy” as the intervention/treatment, excluding those described as suspended, terminated, completed, or withdrawn. Search results, match terms = “gene therapy” in field “Interventions”. https://www.clinicaltrials.gov/ct2/results?intr=gene+therapy&Search=Apply&recrs=m&age_v=&gndr=&type=&rslt=. Accessed 5 Nov 2019.
6. Federal Drug Administration - News and Events. Remarks by Commissioner Gottlieb to the Alliance for Regenerative Medicine's Annual Board Meeting. 2018. <https://www.fda.gov/NewsEvents/Speeches/ucm608445.htm>. Accessed 20 May 2020.
7. EvaluatePharma. Authors' count of gene therapies in phases I, II, III (Accessed 24 Apr 2019).
8. Statement from FDA Commissioner Scott Gottlieb, M.D. and Peter Marks, M.D., PhD., Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies. January 15, 2019. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629493.htm>. Accessed 20 May 2020.
9. Caffrey M. NCCN panel digs into reality of CAR-T cell reimbursement. March 21, 2019. [Internet] <https://www.ajmc.com/conferences/nccn-2019/nccn-panel-digs-into-reality-of-car-t-cell-reimbursement>. Accessed 20 May 2020.
10. Armstrong, M. Novartis and Biogen face spinal muscular atrophy reckoning. April 25, 2019. [Internet] <https://www.evaluate.com/vantage/articles/news/corporate-strategy/novartis-and-biogen-face-spinal-muscular-atrophy-reckoning>. Accessed 20 May 2020.
11. Quinn C, et al. Estimating the clinical pipeline of cell and gene therapies and their potential economic impact on the US health-care system. *Value Health*. 2019;22(6):621–6.
12. Aitken M, Kleinrock M. Medicine use and spending in the U.S.: a review of 2018 and outlook to 2023. IQVIA Institute. 2019. Available at: <https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023>. Accessed 20 May 2020.
13. Hatch–Waxman Drug Price Competition and Patent Term Restoration Act of 1984, P.L. No. 98-417.
14. Bayh–Dole Drug Price Competition and Patent Term Restoration Act of 1980, P.L. 96-517.
15. Stevenson–Wylder Technology Innovation Act of 1980, P.L. 96-480.
16. Grabowski HG, DiMasi JA, Long G. The roles of patents and research and development incentives in biopharmaceutical innovation. *Health Aff*. 2015;2:302–10.

17. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20–33.
18. Grabowski H, Vernon J, DiMasi JA. Returns on research and development for 1990s new drug introductions. *Pharmacoeconomics*. 2002;20(Suppl 3):11–29.
19. Scherer FM. Pharmaceutical innovation. In: Hall B, Rosenberg N, editors. *Handbook of the economics of innovation*, vol. 1. Amsterdam: North-Holland; 2010. p. 539–74.
20. Grabowski H, Vernon J. The distribution of sales revenues from pharmaceutical innovation. *Pharmacoeconomics*. 2000;18(Suppl 1):21–32.
21. Berndt ER, Nass D, Kleinrock M, Aitken M. Decline in economic returns from new drugs raises questions about sustaining innovations. *Health Aff (Millwood)*. 2015;34(2):245–52.
22. Cockburn IM. The changing structure of the pharmaceutical industry. *Health Aff (Millwood)*. 2004;23(1):10–22.
23. IQVIA Institute for Human Data Science. The changing landscape of research and development, April 2019. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-changing-landscape-of-research-and-development.pdf?_=1556058037527. Accessed 20 May 2020.
24. Grabowski H, Long G, Mortimer R, et al. Updated trends in US brand-name and generic drug competition. *J Med Econ*. 2016;19(9):836–44.
25. Biologics Price Competition and Innovation Act of 2009, P.L. 111-148.
26. Biologics Price Competition and Innovation Act of 2009, P.L. 111-148, §262(k)(2)(A).
27. Biologics Price Competition and Innovation Act of 2009, P.L. 111-148, §262(k)(4)(A).
28. Biologics Price Competition and Innovation Act of 2009, P.L. 111-148, §262 (l).
29. Grabowski HG, et al. Biosimilar competition: lessons from Europe. *Nat Rev Drug Discovery*. 2014;13:99–100.
30. “Sandoz Launches Zarxio™ (filgrastim-sndz), the first biosimilar in the United States,” Sandoz, September 3, 2015. <https://www.sandoz.com/news/media-releases/sandoz-launches-zarxiotm-filgrastim-sndz-first-biosimilar-united-states>. Accessed 20 May 2020.
31. “Biosimilar Product Information,” FDA, last updated January 2019, “Center for Drug Evaluation and Research List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date”. <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>. Accessed 19 Jan 2020.
32. Wright BD. The economics of invention incentives: patents, prizes, and research contracts. *Am Econ Rev*. 1983;93(4):691–707.
33. For example, the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, signed into law as part of the 2020 federal budget, strengthens access by generic manufacturers to brand-name drug samples for the purpose of producing generic versions. H.R. 1865: Further Consolidated Appropriations Act. 2020. <https://www.congress.gov/bills/116th-congress/house-bill/1865>. Accessed 20 May 2020.
34. Swagel PL, Director, Congressional Budget Office. Letter to the Honorable Frank Pallone Jr., Chairman, Committee on Energy and Commerce, U.S. House of Representatives, December 10, 2019. Budgetary Effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act.
35. Stiglitz JE. Scrooge and intellectual property rights. *BMJ*. 2006;333(7582):1279–80 (See, for example).
36. The most recent available PhRMA annual membership survey estimates its members (which do not account for all drug companies) spent nearly US\$80 billion on R&D in 2018. <https://www.phrma.org/report/2018-phrma-annual-membership-survey>. Accessed 20 May 2020.
37. Louisiana Department of Health. Gilead’s Asequa Therapeutics selected to partner with health department for hepatitis C drug subscription model. 2019. <http://ldh.la.gov/index.cfm/newsroom/detail/5097>. Accessed 20 May 2020.
38. Cernuschi T, Furrer E, Schwalbe N, Jones A, Berndt ER, McAdams S. Advance market commitment for pneumococcal vaccines: putting theory into practice. *Bull World Health Organ*. 2011;89(12):913–8.
39. Yamey G, Schäferhoff M, Hatchett R, Pate M, Zhao F, McDade K. Ensuring global access to COVID-19 vaccines. *Lancet*. 2020. [https://doi.org/10.1016/S0140-6736\(20\)30763-7](https://doi.org/10.1016/S0140-6736(20)30763-7).
40. Yamey G, Schäferhoff M, Pate M, Chawla M, Ranson K, Zhao F, Hatchett R, Wilder R. Funding the development and manufacturing of COVID-19 vaccines: background paper for the World Bank/CEPI financing COVID-19 vaccine development consultation on February 20, 2020. The Center for Policy Impact in Global Health. Duke Global Working Paper Series: number 20. 2020. <http://centerforpolicyimpact.org/ourwork/our-publications/funding-development-and-manufacturing-of-covid-19-vaccines/>. Accessed 20 May 2020.
41. Kremer M, Williams H. Incentivizing innovation: adding to the tool kit. In: Lerner J, Stern S, editors. *Innovation policy and the economy*, vol. 10. Chicago: University of Chicago Press; 2010. p. 1–17.
42. Bagley N, Chandra A, Garthwaite C, Stern AD. It’s time to reform the Orphan Drug Act. *NEJM Catal*. 2018;4(6).
43. Barlow JF, Yang M, Teagarden JR. Are payers ready, willing, and able to provide access to new durable gene therapies? *Value Health*. 2019;22(6):642–7.
44. Ciarametero M, Long G, Johnson M, Kirson N, Dubois RW. Are payers ready to address the financial challenges associated with gene therapy? *Health Affairs Blog*. 2018. <https://doi.org/10.1377/hblog20180626.330036>.
45. MIT NewDIGS FoCUS Project. Incorporation of value-based payment agreements into the calculation of Medicaid drug rebates. 2019. https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief_2019F201v032%20-%20Medicaid%20Best%20Price_0.pdf. Accessed 20 May 2020.