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Transformative Models to Promote Prescription Drug Innovation and Access: A Landscape Analysis

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Transformative Models to Promote Prescription Drug Innovation and Access: A Landscape Analysis

Phebe Hong, Aaron S. Kesselheim & Ameet Sarpatwari*

Abstract:

The patent-based pharmaceutical innovation system in the US does not incentivize the development of drugs with the greatest impact on patient or public health. It has also led to drug prices that patients and health care systems cannot afford. Three alternate approaches to promoting pharmaceutical innovation have been proposed to address these shortcomings. Delinkage models involve payments for drug innovation based on public health value rather than on a per-use basis. Public manufacturing models call upon governments and nonprofit organizations to lead drug discovery, development, and production. Public-private partnership models entail publicly-funded organizations working closely with for-profit partners on drug development and price-setting. Each model exhibits promise in promoting prescription drug innovation and access. This paper reviews these transformative models in detail, examining their key characteristics, advantages, and limitations.

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INTRODUCTION

Pharmaceutical innovation is critical for patient care and public health, as drugs can be among the most effective—and cost-effective—interventions that physicians can offer. However, drug development is also long and expensive. To attract private investment in this endeavor, the US federal government provides 20-year patents and other long-lasting statutory market exclusivities that give companies time to earn back up-front investments and make profits.¹ During this market exclusivity period, manufacturers can charge whatever they want, so US prices typically far exceed those for the same drugs sold in other high-income countries.²

This innovation model has been criticized on two grounds. First, it does not incentivize the development of drugs with the greatest impact on patient or public health,³ but rather encourages private investment in drugs that are likely to generate the greatest revenues. As a result, despite being sold at high prices, many new drugs that receive US Food and Drug Administration (FDA) approval do not offer important advances in efficacy or safety. For example, among new drugs approved in 2017 in the US, about one-third were rated by expert organizations in Germany, France, and Canada to offer no or minor additional benefits over existing treatments.⁴ Another study found that 40% of the highest-spending brand-name drugs in Medicare were reformulations of previously approved active ingredients.⁵

Second, the current pharmaceutical innovation model leads to prices of brand-name drugs that patients and health care systems cannot afford. For example, when the direct-acting antiviral sofosbuvir (Sovaldi) was approved by the FDA in 2013, it offered for the first time the possibility of a cure for chronic hepatitis C virus infection, an infectious disease affecting 3-4 million US patients.⁶ But because Gilead priced the product at \$84,000 for a standard 12-week course of therapy, payers like Medicaid were unable to offer it to all qualifying patients due to

1. See Aaron S. Kesselheim, Michael S. Sinha & Jerry Avorn, *Determinants of Market Exclusivity for Prescription Drugs in the United States*, 177 JAMA INTERNAL MED. 1658, 1659 (2017).

2. See Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 860 (2016).

3. See Anna Kaltenboeck et al., *Grounding Value-Based Drug Pricing in Population Health*, 107 CLINICAL PHARMACOLOGY & THERAPEUTICS 1290, 1291 (2020).

4. Richard G. Frank, Jerry Avorn & Aaron S. Kesselheim. *What Do High Drug Prices Buy Us?* HEALTH AFFAIRS BLOG (April 29, 2020), <https://www.healthaffairs.org/doi/10.1377/hblog20200424.131397/full> [https://perma.cc/LZ2A-QUL4].

5. Emily H. Jung, Ameet Sarpatwari & Aaron S. Kesselheim, *Novelty of Active Ingredients in High-Cost Brand-Name Drugs*, J. GEN. INTERNAL MED. 1, 1 (2020).

6. See Andrew Pollack, *F.D.A. Approves Pill to Treat Hepatitis C*, N.Y. TIMES (Dec. 6, 2013), <https://www.nytimes.com/2013/12/07/business/fda-approves-pill-to-treat-hepatitis-c.html> [https://perma.cc/2BLG-YFYA].

concerns that it would exceed their drug budgets.⁷ As a result, only 2.4% of eligible Medicaid patients were treated in the first year.⁸ Although prices of direct-acting antivirals have declined in recent years due to competition, they remain high, with many patients still unable to access treatment.⁹ The sofosbuvir case was particularly controversial because the drug emerged from years of publicly-funded research and development at Emory University, followed by work at a small company founded by academic scientists, before being transferred to Gilead for the final steps in development just a year before approval.¹⁰

To promote the discovery of more innovative drugs like sofosbuvir while ensuring wider access after approval, three alternate models of drug development have been suggested: first, a “delinkage” model in which payment for drug innovation is made based on its public health value rather than on a per-use basis; second, a “public manufacturing” model, in which the government or nonprofit organizations fund the entire discovery and development process and then price drugs closer to the cost of production; and third, a “public-private partnership” model, in which a publicly-funded organization that discovers a new drug would transfer intellectual property to the private market, but remain closely involved in the drug development and price-setting process.

Key values should guide assessment of these models. The current patent-based system has some strengths, including incentives that directly benefit innovators and timely invention disclosures. An ideal model would preserve these advantages, while encouraging greater needs-driven innovation, transparency, efficiency, and affordability. With these values in mind, we review delinkage, public manufacturing, and public-private partnership models in detail, examining their advantages and limitations.

I. THE DELINKAGE MODEL

While many variations of delinkage models exist, the term delinkage is often

7. See Soumitri Barua et al., *Restrictions for Medicaid Reimbursement of Sofosbuvir for the Treatment of Hepatitis C Virus Infection in the United States*, 163 ANNALS INTERNAL MED. 215, 215 (2015).

8. Joshua M. Liao & Michael A. Fischer, *Restrictions of Hepatitis C Treatment for Substance-Using Medicaid Patients: Cost Versus Ethics*, 107 AM. J. PUB. HEALTH 893, 896 (2017).

9. See Ed Silverman, *Most State Medicaid Programs Continue to Restrict Access to Hepatitis C Medicines*, STAT (Oct. 16, 2019), <https://www.statnews.com/pharmalot/2019/10/16/medicaid-hepatitis-access-drug-prices/> [<https://perma.cc/JVX9-28RG>].

10. Merrill Goozner, *Why Sovaldi Shouldn't Cost \$84,000*, MODERN HEALTHCARE (May 3, 2014), <https://www.modernhealthcare.com/article/20140503/MAGAZINE/305039983/why-sovaldi-shouldn-t-cost-84-000> [<https://perma.cc/9NXJ-REWU>]; see also WILLIAM RICE & FRANK CLEMENTE, GILEAD SCIENCES: PRICE GOUGER, TAX DODGER 1, 14 (July 2016), <https://americansfortaxfairness.org/files/ATF-Gilead-Report-Finalv3-for-Web.pdf> [<https://perma.cc/4UCJ-NX2Q>].

used synonymously with “innovation inducement prizes” and “market entry rewards.”¹¹ Conceptually, delinkage refers to the separation of an innovator’s research and development costs from the price of its products, which is achieved by rewarding the innovator directly for the innovation rather than indirectly through market exclusivity.¹² In this manner, delinkage systems reduce or eliminate an innovator’s reliance on sales to recuperate research and development investments and earn profits.¹³

Proponents of delinkage contend that it would benefit patients by lowering prices and increasing access to drugs.¹⁴ Some delinkage proposals require innovators to forfeit their patents in exchange for the rewards, allowing immediate generic entry to drive down drug prices.¹⁵ Other proposals allow innovators to retain their patents, but contractually obligate innovators to supply their drugs close to the marginal cost of production.¹⁶

Delinkage also promotes innovation by ensuring the financial attractiveness of developing desired drugs. Rewards provide innovators with predictability, guaranteeing a return on investment upon meeting stated goals,¹⁷ which can be tailored to favor certain innovation outcomes, such as developing drugs for unmet needs.¹⁸ Even the pharmaceutical industry has acknowledged the benefits of delinking financial revenues from sales, given the mitigation of financial risk for both innovators and health care systems.¹⁹ Delinkage models could also increase the overall efficiency of the system by eliminating the need for substantial manufacturer spending on marketing efforts, which currently accounts for \$30

11. See JAMES LOVE, UNITAID, AN ECONOMIC PERSPECTIVE ON DELINKING THE COST OF R&D FROM THE PRICE OF MEDICINES 1, 14 (2016), http://www.unitaid.org/assets/Delinkage_Economic_Perspective_Feb2016.pdf [<https://perma.cc/SJ4X-PUT4>].

12. U.N. Secretary General and Co-Chairs of the High-Level Panel, *Report of the United Nations Secretary-General’s High-Level Panel on Access to Medicine: Promoting Innovation and Access to Health Technologies* (Sept. 2016) (defining delinkage), <http://www.unsgaccessmeds.org/s/UNSG-HLP-Report-FINAL-12-Sept-2016.pdf> [<https://perma.cc/Z4AK-5GDH>].

13. GREGORY W. DANIEL ET AL., DUKE MARGOLIS CENTER FOR HEALTH POLICY, VALUE-BASED STRATEGIES FOR ENCOURAGING NEW DEVELOPMENT OF ANTIMICROBIAL DRUGS 7 (2017) [hereinafter Duke Margolis Report].

14. LOVE, *supra* note 11, at 15.

15. See Kevin Outterson et al., *Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality*, 13 PLOS MEDICINE 1, 4 (2016).

16. *See id.* at 4–5.

17. John H. Rex & Kevin Outterson, *Antibiotic Reimbursement in a Model Delinked from Sales: A Benchmark-based Worldwide Approach*, 16(4) LANCET INFECTIOUS DISEASES 500, 504 (2016).

18. LOVE, *supra* note 11, at 24.

19. *Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance* 1, 3 (Jan. 2016), https://www.abpi.org.uk/media/1675/industry_declaration_on_combating_antimicrobial_resistance_jan2017.pdf [<https://perma.cc/6QHD-BQ96>].

billion per year.²⁰

Finally, delinkage models are particularly beneficial for specific drugs, such as antibiotics, which require post-approval restrictions on use.²¹ In the current system, revenues are dependent on sales, encouraging innovators to maximize utilization during patent-protected periods, exacerbating the threat of antimicrobial resistance.²²

Critics of delinkage models point to the financial challenges of using nonmarket exclusivity rewards to incentivize research and development. Such rewards must be sufficiently large to offset the high risk of failure innovators bear to develop successful drugs. Governments may find it difficult to determine optimal reward pricing to achieve innovation, due to under- or over-valuation of research and development costs.²³ For example, estimates of the reward needed to incentivize the development of an innovative antibiotic range from \$919 million to \$5 billion.²⁴ Furthermore, governments would have to fund not only the rewards, but also the administrative costs to implement the schemes.²⁵ The difficulty in funding such efforts is exemplified by the World Health Organization Global Observatory on research and development, established in 2013. Many of its projects, including a nano-based malaria drug delivery system, were ultimately cancelled due to underfunding.²⁶

Some innovators further argue that delinkage models are too risky and may not motivate appropriate actors. A one-time upfront payment for a promising drug may be a waste of resources if the drug is later determined to be less effective than originally predicted or to have safety issues that require it to be removed from the market. As FDA regulatory approval of new drugs has increasingly occurred based on less data and less rigorous study designs,²⁷ the risk of such an outcome has increased. Additionally, pharmaceutical innovation often happens in multiple settings in parallel. If a prize is only awarded to a limited set of winners, multiple innovators may be discouraged from participating given uncertainty of being the

20. Lisa M. Schwartz & Steven Woloshin, *Medical Marketing in the United States, 1997-2016*, 321 JAMA 80, 80 (2019).

21. David Holmes, *Report Urges Controversial 'Delinkage' to Foster New Antibiotics*, 20 NATURE MED. 320, 320 (2014).

22. CHATHAM HOUSE REPORT: TOWARDS A NEW GLOBAL BUSINESS MODEL FOR ANTIBIOTICS DELINKING REVENUES FROM SALES (Charles Clift et al. eds., 2015).

23. PHILIP STEVENS, *DELINKED FROM REALITY 5* (Nov. 2017), <https://geneva-network.com/wp-content/uploads/2017/11/Delinkage.pdf> [<https://perma.cc/S99G-CSRW>].

24. Rex & Outterson, *supra* note 17, at 501.

25. See STEVENS, *supra* note 23, at 4; but see LOVE, *supra* note 11, at 22 (concluding that a delinkage approach to drug development would be Pareto efficient and would not result in deadweight loss).

26. STEVENS, *supra* note 23, at 11.

27. Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Approval and Regulation of Pharmaceuticals, 1983-2018*, 323 JAMA 164, 164 (2020).

first to the finish line.²⁸ However, the second or third drug to enter the market in a class may offer important utility for patients.²⁹

Opposition to delinkage also stems from its centrally-planned nature that some commentators fear will result in “rent-seeking and crony capitalism.”³⁰ According to this logic, a delinkage system that gives government officials discretion to direct drug development would be susceptible to regulatory capture by special interests as well as changing political and economic tides.³¹ To mitigate the effects of politicization, several delinkage proposals suggest entrusting the execution of reward schemes to neutral “pipeline coordinators” or well-established administrative agencies, such as the National Institutes of Health (NIH).³²

Finally, lack of international cooperation could be a barrier to successful deployment of delinkage models. The top-selling drugs in the world earn billions of dollars per year in revenue.³³ Thus, the size of payments required to stimulate innovation may require global coordination, consensus, and priority alignment, which is challenging to accomplish.³⁴ Some commentators have proposed that a core group of countries with high levels of clinical research activity could initially pilot a delinkage model,³⁵ with a newly established secretariat or global organization charged with leading the effort.³⁶

A. Characteristics of Delinkage Models

Several working groups and international organizations in the US and Europe have formulated proposed delinkage models (Table 1).³⁷ The majority seek to incentivize development of new drugs to combat antimicrobial-resistant infections. However, some delinkage models outside of antibiotics have also been conceived,

28. CHANTAL MOREL, REACT, EXPLORING RESPONSES TO THE NEED FOR NEW ANTIBIOTICS: HOW DO DIFFERENT INCENTIVES COMPARE? 6 (2011).

29. See, e.g., Jing Luo et al., *Effect of Generic Competition on Atorvastatin Prescribing and Patients’ Out-of-Pocket Spending*, 176 JAMA INTERNAL MED. 1317, 1317 (2016).

30. STEVENS, *supra* note 23, at 8.

31. See MOREL, *supra* note 28, at 7.

32. See CHRISTINE ÅRDAL ET AL., DRIVE-AB, REVITALIZING THE ANTIBIOTIC PIPELINE: STIMULATING INNOVATION WHILE DRIVING SUSTAINABLE USE AND GLOBAL ACCESS 5 (2018) [hereinafter DRIVE-AB Report]; see also Improving Access to Affordable Prescription Drugs Act, S. 771, 115th Cong. (2017) [hereinafter IAAPD Act].

33. See IQVIA INSTITUTE, MEDICINE USE AND SPENDING IN THE U.S. (May 9, 2019), <https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023> [https://perma.cc/FG5X-ZR8P].

34. See Kimberly Sciarretta et al., *Economic Incentives for Antibacterial Drug Development: Literature Review and Considerations from the Transatlantic Task Force on Antimicrobial Resistance*, 63 CLINICAL INFECTIOUS DISEASES 1470, 1473 (2016).

35. See CHATHAM HOUSE REPORT, *supra* note 22, at 31.

36. See *id.*

37. MOREL, *supra* note 28, at 7.

such as the Cancer Innovation Fund.³⁸ In this section, we review the key characteristics of identified delinkage models.

1. Drug Criteria

Organizations charged with implementing delinkage programs must first establish guidance to innovators specifying what requirements drugs must meet to qualify for rewards, including clear efficacy and safety standards. These “target profile criteria” should be specific enough to provide innovators with predictability and should be fixed for several years to account for lengthy research and development times. However, they should also be flexible enough to incorporate unanticipated discoveries in the innovation process and periodically updated to reflect changing unmet needs.³⁹

For example, in the antibiotic context, groups such as Knowledge Ecology International, Chatham House, and DRIVE-AB recommend that target product profile design should be guided by assessing unmet public health needs for antibiotic innovation.⁴⁰ Chatham House recommends that delinkage program administrators conduct comprehensive global threat assessments to identify incentive targets, similar to the antimicrobial resistance threat assessment conducted by the Centers for Disease Control and Prevention (CDC) in 2013.⁴¹ The CDC’s assessment used various criteria, including incidence and prevalence, clinical impact attributable to infection, economic impact, transmissibility, preventability through public health measures, and availability of effective treatment.⁴² Alternatively, DRIVE-AB suggests prioritizing antibiotic development based on existing lists, such as the World Health Organization’s list of priority pathogens.⁴³ Target product profiles developed from these lists would ideally define specifications for safety and efficacy requirements, indications, dosing, treatment duration, and route of administration, which current proposals generally fail to do.

2. Degree of Delinkage

Delinkage models can be fully or partially delinked. In a fully delinked system, innovator profits are derived solely from reward payments, not sales.⁴⁴ The

38. Cancer Innovation Fund (2017), <https://imedproject.org/proposals-database/cif/> [<https://perma.cc/4KZ5-PP42>] (last visited Aug. 17, 2019).

39. DRIVE-AB Report, *supra* note 32, at 10.

40. *See id.*; CHATHAM HOUSE REPORT, *supra* note 22, at 12.

41. CHATHAM HOUSE REPORT, *supra* note 22, at 12.

42. *See id.*

43. DRIVE-AB Report, *supra* note 32, at 24.

44. *See* MATTHEW RENWICK, DAVID FINDLAY & SILAS HOLAND, AN APPROACH TO DESIGNING

drug is supplied at a price that reflects the marginal cost of production. By contrast, a partially delinked system awards innovators with smaller reward payments, and allows them to continue receiving revenue from sales, subject to negotiated price or quantity conditions.⁴⁵

The majority of delinkage proposals that we identified, including those by the Review on Antimicrobial Resistance, the Transatlantic Task Force on Antimicrobial Resistance, and the Norway Pilot Study, use partially rather than fully delinked models.⁴⁶ Some commentators argue that partial delinkage is simpler to implement within existing reimbursement systems, minimizing disruptive market effects. Additionally, by retaining revenues from sales, innovators remain engaged in the lifecycle of their product. Partial delinkage may also be more feasible and sustainable for governments to implement, given the likely limited size of reward payments they could offer.⁴⁷ The Boston Consulting Group recommends a slight variation of the partially delinked model—the “insurance mechanism”—which requires innovators to return a percentage of their profits up to the original amount of the market entry reward.⁴⁸ However, full delinkage models would more effectively accomplish the goals of containing spending and promoting more equitable access by eliminating the innovator’s involvement in pricing and ability to profit through sales.

3. Intellectual Property

In delinkage models, innovators’ drug patents can be purchased outright, licensed, or retained.⁴⁹ In a full patent buyout, the government purchases the innovators’ drug patents and then supplies the drug at prices close to marginal cost (or alternatively, licenses the intellectual property competitively to generic manufacturers). By contrast, in a partial patent buyout, innovators license their drug patents to the government in exchange for reward payments. The government is then able to establish market prices for those drugs. Finally, under marginal cost procurement contracts, innovators retain their intellectual property but supply the drug at contractually arranged prices.

MARKET ENTRY REWARDS FOR STIMULATING ANTIBIOTIC DEVELOPMENT, DRIVE-AB (2017).

45. *See id.*

46. JIM O’NEILL, REVIEW ON ANTIMICROBIAL RESISTANCE, SECURING NEW DRUGS FOR FUTURE GENERATIONS: THE PIPELINE OF ANTIBIOTICS 21 (2015); Christine Årdal et al., *Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance*, 65(8) CLINICAL INFECTIOUS DISEASES 1378, 1381 (2017) [hereinafter TATFAR Report]; Christine Årdal et al., *Designing a Delinked Incentive for Critical Antibiotics: Lessons from Norway*, 46 J. LAW, MED. & ETHICS 43, 47 (2018) [hereinafter Norway Pilot Study].

47. Duke Margolis Report, *supra* note 13, at 8.

48. BOSTON CONSULTING GROUP, BREAKING THROUGH THE WALL: A CALL FOR CONCERTED ACTION ON ANTIBIOTICS RESEARCH AND DEVELOPMENT 40 (2017).

49. *See* Outtersen et al., *supra* note 15, at 5.

Thus, the critical component with any intellectual property scheme in a delinked system is that the rewards ultimately replace or eliminate market exclusivity. In comparing the schemes outlined above, the full patent buyout would require the government to offer substantially higher reward payments given the historical reluctance of pharmaceutical manufacturers to part with their intellectual property.⁵⁰

4. *Payment Schedule*

Reward payments in delinkage models can be issued in various ways. One option is to pay the innovator an upfront lump sum payment shortly following market approval. However, such payments carry high risk because evidence of clinical value may be insufficient at the time of approval, especially for drugs approved based on changes in biomarkers or other unproven surrogate endpoints rather than clinically meaningful effects.⁵¹

Another option is milestone payments, awarded to innovators upon meeting key goals during development or following market approval. Upstream payments during development are highly valuable to innovators investing in large clinical trials but pose risk to funders.⁵² Outtersen et al. recommend a staged approach, in which a base reward is granted upon drug approval, with subsequent annual payments awarded based on evaluation of effectiveness data collected in the course of usual care.⁵³ The annual payments would aid the innovator in financing manufacturing and supply-chain availability. Rex et al. and the Duke Margolis Center propose a similar scheme that would award innovators with increases to each “benchmark payment” based on desirable factors, such as proof of a novel mechanism of action, addressing serious unmet needs, reducing health care costs, targeting resistant pathogens, or label expansions to other indications.⁵⁴

5. *Reward Obligations*

Delinkage models can also include additional obligations for manufacturers in exchange for reward payouts. Examples include guaranteed supply of drugs and open-source information sharing of clinical data.⁵⁵ To combat overuse, delinkage models for antibiotics can include conditions on marketing and promotion.⁵⁶ For example, the Improving Access to Affordable Prescription Drugs Act, proposed in

50. See MOREL, *supra* note 28, at 8.

51. See Sciarretta et al., *supra* note 34, at 1472.

52. See CHATHAM HOUSE REPORT, *supra* note 22, at 4.

53. Outtersen et al., *supra* note 15, at 4.

54. Rex & Outtersen, *supra* note 17, at 502; Duke Margolis Report, *supra* note 13, at 12.

55. See LOVE, *supra* note 11, at 48.

56. See Outtersen et al., *supra* note 15, at 5.

Congress in 2017, would have established an Antibiotic Prize Fund offering prizes conditional on waiver of patent rights, reasonable pricing, reports of marketing activity, and data disclosures.⁵⁷

6. Reward Size

A main challenge for delinkage model implementation is determining the magnitude of payments necessary to attract interest from private investors and for-profit companies. The payments must be large enough to motivate companies to participate but feasible for governments to finance. Proposals suggest that reward size could be estimated based on standard health technology assessments, social value of the subject of the prize fund to health systems, or general global market demand.⁵⁸ The BEAM Alliance, a network of European biopharmaceutical companies, issued a statement that innovators would be more willing to participate in delinkage schemes if the reward amount “ultimately allows a fair redistribution to those who innovated and took the initial risk to bring the science through early and clinical stages.”⁵⁹

The President’s Council of Advisors on Science and Technology report, the United Kingdom’s Antimicrobial Resistance review, and the DRIVE-AB report all estimate that prizes in the range of \$1 billion (in addition to sales) would be required in the antibiotic market.⁶⁰ It was estimated that a reward of this amount could quadruple the number of novel antibiotics over the next 30 years.⁶¹

Although such prizes may be costly upfront, delinkage systems could ultimately lead to substantial savings for health care systems by reducing or eliminating premiums normally imposed by innovators on drugs. For example, an analysis of Senator Bernie Sanders’ (I-VT) proposed Medical Innovation Prize Fund, which would allocate 0.55% of US GDP to reward health outcomes in a delinked model, estimated that it would have saved \$92 billion in 2016.⁶² Additionally, increased availability and access to novel drugs could—if effective—lower total health care costs by preventing costlier downstream use of health care resources.

57. IAAPD Act, *supra* note 32, at 77.

58. See Outterson et al., *supra* note 15, at 4.

59. BEAM ALLIANCE, KEY GUIDELINES TO IMPLEMENT EFFECTIVE MEASURES TOWARD SMES TO REVIVE THE ANTIBACTERIAL R&D FIELD 14 (2017).

60. See PRESIDENT’S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY, REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE 6 (2014) [hereinafter PCAST Report]; O’Neill, *supra* note 46, at 20; DRIVE-AB Report, *supra* note 32, at 6.

61. DRIVE-AB Report, *supra* note 32, at 6.

62. *Savings*, KNOWLEDGE ECOLOGY INT’L (2018), <https://delinkage.org/savings/> [https://perma.cc/F5YL-KATW] (last visited Aug. 13, 2019).

7. Funding Sources

Given the substantial resources needed to finance a delinkage model, commentators have suggested a broad range of potential funding sources. The most commonly cited are government health care budgets and higher insurance premiums.⁶³ Several proposals recommend the creation of international funds supported by contributions from multiple countries.⁶⁴ According to one estimate, between \$4 and \$5 billion could be raised if Organization for Economic Cooperation countries each contributed 0.01% of their GDPs.⁶⁵ Taxes could be imposed on certain prescriptions (e.g., a usage fee on all antibiotics to fund a reward pool for novel antibiotic drugs).⁶⁶ Finally, a competitive financing scheme has also been proposed in which individuals and employers would be required to contribute to pooled research and development funds managed by investment intermediaries.⁶⁷

B. Outcomes from Delinkage Models

Despite numerous proposals, there has been no large-scale implementation of delinkage models for drug development (Table 2).⁶⁸ However, several smaller, targeted prize competitions have launched. For example, the Longitude Prize, established in the United Kingdom in 2014, offers a £10 million prize fund for an accurate and affordable rapid point-of-care diagnostic test that would conserve antibiotic use.⁶⁹ No one has won it. Other biomedical prize competitions include the International AIDS Vaccine Initiative Challenge (protein research), the TB Alliance Challenge (drug production), the Archon Genomics X Prize (genome sequencing), and the CASP Prize (protein structure prediction).⁷⁰

63. See CHATHAM HOUSE REPORT, *supra* note 22, at 7.

64. See *id.* at 16.

65. See Outterson et al., *supra* note 15, at 2–3.

66. See PCAST Report, *supra* note 60, at 41.

67. Tim Hubbard & James Love, *A New Trade Framework for Global Healthcare R&D*, 2 PLoS BIOLOGY 147, 150 (2004).

68. See MOREL, *supra* note 28, at 7.

69. LONGITUDE PRIZE, <https://longitudeprize.org/> [<https://perma.cc/E5DY-G6QK>] (last visited Aug. 13, 2019).

70. See *IAVI Posts \$150,000 Challenge on InnoCentive*, INTERNATIONAL AIDS VACCINE INITIATIVE (Dec. 17, 2008), <https://www.iavi.org/news-resources/press-releases/2008/iavi-posts-150-000-challenge-on-innocentive> [<https://perma.cc/XCE8-YU2Y>]; *A Global Effort to Reduce the Costs of a TB Drug Candidate*, TB ALLIANCE (Nov. 6, 2008), <https://www.tballiance.org/news/global-effort-reduce-costs-tb-drug-candidate> [<https://perma.cc/5PLV-SGG7>]; Peter Diamandis, *Outpaced by Innovation: Canceling an XPRIZE*, HUFFPOST (Aug. 22, 2013), https://www.huffpost.com/entry/outpaced-by-innovation-ca_b_3795710 [<https://perma.cc/S7PH-TKfV>]; Robert F. Service, *Google's DeepMind Aces Protein Folding*, SCIENCE MAGAZINE (Dec. 6, 2018), <https://www.sciencemag.org/news/2018/12/google-s-deepmind-aces-protein-folding> [<https://perma.cc/48H7-JAXM>].

The closest mechanisms to large-scale drug development delinkage models that have been implemented are advanced market commitments, which involve contracting ahead of time to buy products meeting specified conditions.⁷¹ The guaranteed purchase order is the prize. In 2007, with support from five countries and the Bill and Melinda Gates Foundation, the GAVI alliance established a \$1.5 billion advanced market commitment fund to subsidize purchases of qualified pneumococcal vaccines in developing countries.⁷² However, the fund was later criticized for having minimal influence on innovation, since manufacturers had already developed the vaccines prior to program implementation.⁷³ Another advanced market commitment is guaranteed volume purchases of childhood vaccines that the US government offers to ensure a stable supply of products that have vital importance to public health.⁷⁴

Delinkage-like models have been implemented in other sectors, including the defense, electric utility, and academic publishing industries.⁷⁵ A McKinsey study found an increase in innovation prize competitions in recent decades, noting a shift to providing incentives for specific rather than broad categories of innovation.⁷⁶ Among them are the X Prizes, a series of philanthropically-funded contests started by Peter Diamandis in 1995. The Ansari X Prize, the first such prize, offered a \$10 million reward for the development of a spacecraft capable of carrying three people into space twice within ten days.⁷⁷ The first-place team spent more than \$20 million to develop their winning spacecraft, while total spending by all competing teams exceeded \$100 million.⁷⁸ Although the competition was successful in generating publicity for the sector, the large investment-to-prize ratio highlighted the challenge of prize tailoring. By contrast, the Ashoka's Changemakers competitions, a series of contests focused on various social issues, awards smaller

71. Kevin Outterson & Aaron S. Kesselheim, *Market-Based Licensing for HPV Vaccines in Developing Countries*, 27 HEALTH AFFAIRS 130, 132 (2008).

72. *About the Pneumococcal Vaccine*, GAVI: The Vaccine Alliance, <https://www.gavi.org/investing/innovative-financing/pneumococcal-amc/about/> [<https://perma.cc/8DHR-BWUV>] (last visited Aug. 13, 2019).

73. See, e.g., Jens Plahte, *Is the Pneumococcal Vaccine Advance Market Commitment Motivating Innovation and Increasing Manufacturing Capacity? Some Preliminary Answers*, 30 VACCINE 2462, 2462 (2012).

74. See Alan R. Hinman, Walter A. Orenstein & Lance Rodewald, *Financing Immunizations in the United States*, 38 CLINICAL INFECTIOUS DISEASES 1440, 1440 (2004).

75. See CHATHAM HOUSE REPORT, *supra* note 22, at 9.

76. Jonathan Bays, Tony Goland & Joe Newsum, *Using Prizes to Spur Innovation*, MCKINSEY & CO. (July 2009), <https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/using-prizes-to-spur-innovation> [<https://perma.cc/3GRA-SW7L>].

77. *Launching a New Space Industry*, <https://www.xprize.org/prizes/ansari> [<https://perma.cc/MWF9-TZHB>] (last visited Mar. 7, 2020).

78. William A. Masters & Benoit Delbecq, *Accelerating Innovation with Prize Rewards*, INT'L FOOD POL'Y RES. INST. 8 (Dec. 2008).

prize amounts (around \$5,000).⁷⁹ The competition has been successful in fostering collaboration among competitors in online forums, resulting in the generation of novel ideas.⁸⁰

In general, commentators note that critical characteristics of effective prize competitions are clear and measurable objectives, a credible guarantee of payment, and impartial judges.⁸¹ Typical shortcomings include a lack of incentives for improvements above a certain threshold and the failure of sponsors to evaluate the impact of prizes on innovation and development.⁸²

C. Conclusions and Recommendations

The first steps in implementing a delinkage model for drug development would be to create a prioritization scheme and a well-defined target product profile. Other important details that must be worked out include:

- Defining model elements (e.g., full or partial delinkage, lump sum or milestone payments) that can gain consensus across government and industry stakeholders.
- Determining innovation-incentive prizes or market entry rewards large enough to affect new drug development.
- Identifying a suitable authority to coordinate and implement an international delinkage model.

Some drug manufacturers have already demonstrated their opposition to delinkage concepts and studies.⁸³ In response, several reports recommend that delinkage models remain voluntary, such that manufacturers can either opt-in to receive reward payments or retain their intellectual property rights.⁸⁴ However, it is unknown whether a delinkage reward model could coexist within the current patent-based system.

Since existing delinkage model proposals have predominantly targeted antimicrobial resistance, implementing a delinkage model for antibiotic development initially would be a logical start. Other possible early targets for such

79. ASHOKA CHANGEMAKERS, <https://www.ashoka.org/en-us/program/ashoka-changemakers> [<https://perma.cc/K7BA-3XN5>] (last visited Mar. 7, 2020).

80. See Bays, Goland & Newsum, *supra* note 76.

81. See *id.*; Masters & Delbecq, *supra* note 78, at 9.

82. See Bays, Goland & Newsum, *supra* note 76; Masters & Delbecq, *supra* note 78, at 10.

83. Catherine Saez, *Draft Cancer Resolution Might Be Set For Approval At World Health Assembly*, INTELLECTUAL PROP. WATCH (May 19, 2017), <https://www.ip-watch.org/2017/05/19/draft-cancer-resolution-might-set-approval-world-health-assembly/> [<https://perma.cc/W4EK-Y76K>] (reporting that drug companies were able to block a feasibility study of delinkage in a cancer prevention resolution).

84. Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J. LAW & ECON. 525, 525 (2001).

models are tropical diseases, which are highly prevalent in low-income countries and thus do not attract a lot of investment from international for-profit manufacturers. After collecting data and evaluating the outcomes from these models, delinkage could then be expanded to other therapeutic areas of unmet need. Smaller pilot studies of delinkage models could eventually lead to an alternative system to the current patent-based model of drug development.

TABLE 1: SELECTED PROPOSED DELINKAGE MODELS

Proposal	Description
Antimicrobial Resistance Review	A partially delinked model that awards \$1 billion to cover research and development costs but continues to allow innovators to sell their drug for profit. Payment is conditional upon stewardship and global access.
BEAM Alliance Position Paper	A partially delinked “calibrated” model that awards innovators with payments to supplement value-based payments from payers. Prizes are based on flexible target product profiles and awarded for various milestones, even in the early stages of research and development.
Boston Consulting Group Report	A partially delinked model that awards \$1 billion to antibiotics meeting predefined target product profiles, paid in installments over eight years after approval. Recipients return 30% of their profits (up to \$1 billion). Payments are conditional on access, quality, and stewardship conditions.
Cancer Innovation Fund	A series research and development incentive models, including milestone prizes, end-product prizes, and open source dividends. Once a qualified product obtains approval, a panel awards prizes to entities for having shared knowledge, data, and technology to develop the product.
Chatham House Report	Rewards offered to antibiotics prioritized by global threat assessments. Financial participation begins among a core group of countries, coordinated by an international secretariat to manage pooled funding. The secretariat enters contracts, acquires full intellectual property rights, or establishes licenses with innovators.

Davos Declaration	An agreement among stakeholders in the pharmaceutical industry to support delinkage models that reduce the link between revenues and sales and mitigate financial risk for innovators and health systems.
DRIVE-AB Report	A partially delinked model that awards \$1 billion to antibiotics meeting predefined target product profiles, paid in installments over five years after approval. Payments are conditional upon product's sustainable use and equitable availability.
Duke Margolis PAVE Award	A partially delinked model that awards prizes to qualified antibiotics for the first few years following market approval. By the fifth- or sixth-year, funding is transitioned to value-based contracts with payers. Initial payments are conditional upon innovators demonstrating an increasing share of revenue is sourced from value-based contracts every year.
Improving Access to Affordable Prescription Drugs Act	A \$2 billion antibiotics prize fund that awards monetary prizes to innovators with qualified antibiotics based on criteria established by the NIH Director. Prizes are conditional upon waived patent rights, reasonable prices, marketing reports, and data disclosures.
Life Prize	An open collaborative research and development framework aimed to create an affordable, short-course treatment regimen effective against all forms of tuberculosis. Prizes are awarded to drugs in clinical trials that fulfill predefined criteria, including data and intellectual property sharing.
Medical Innovation Prize Fund	A prize fund equal to 0.55% of gross domestic product overseen by a Board of Trustees, which awards companies for certain drug approvals or interim milestones. The fund is funded by a fee on health insurers.
Norway Pilot Study	A partially delinked model that awards innovators "top-up payments" to supplement revenues from sales. Pilot study researchers determined that a partial delinkage model would be simpler to adapt to existing systems than a full delinkage model.

TRANSFORMATIVE MODELS

OECD Report	A comprehensive approach for incentivizing antibiotic development using various delinkage mechanisms, including monetary prizes, milestone prizes, and full patent buyouts for successfully developed products.
Outterson et al.	A delinked incentive framework involving marginal cost procurement contracts, partial buyout, or full buyout of an innovator's intellectual property. Payments are conditional upon rational use (e.g., no overmarketing or overselling).
PCAST Report	A fund that provides advance market commitments and milestone payments to incentivize antibiotic development. The government provides incentive payments of about \$400 million per drug.
Rex et al.	A fully delinked model that awards \$1 billion awarded to qualified antibiotics, paid in benchmark payments of \$200 million per year over 5 years. Five conditions could increase benchmark payments: novel mechanism of action, addressing unmet medical needs, reducing health care costs, targeting priority resistant pathogens, and post-approval label changes to expand indications.
TATFAR Report	A partially delinked "market-priced" model that awards innovators with small reward payments (~\$500 million) to complement revenues from unit sales. Payments are conditional upon sustainable use and access stipulations.

TABLE 2: SELECTED IMPLEMENTED DELINKAGE MODELS

Model	Description
Archon Genomics X Prize	A \$10 million prize awarded to "the first team to rapidly, accurately and economically sequence 100 whole human genomes to an unprecedented level of accuracy." The competition was later cancelled as it was "outpaced by innovation."

CASP Prize	A competition for protein structure prediction occurs every two years. In December 2018, Google subsidiary Deepmind's AI system AlphaFold won the competition.
International AIDS Vaccine Initiative Challenge	IAVI and InnoCentive offered a \$150,000 prize to the first researcher to design and create a mimic of a stable functional HIV envelope protein to aid in HIV vaccine development. Despite more than 300 responses, no submissions met the challenge requirements.
Longitude Prize	A £10 million prize fund (£8 million payout) for an accurate and affordable rapid point-of-care diagnostic test that conserves antibiotic use. The first team to be selected by the Longitude Committee by 2020 wins the prize.
TB Alliance	The TB Alliance, InnoCentive, and the Rockefeller Foundation awarded two winning teams \$20,000 each for developing a simpler and safer method of producing a tuberculosis drug candidate PA-824.

II. THE PUBLIC MANUFACTURING MODEL

Public manufacturing refers to the development and production of drugs by (or on behalf of) a government or nonprofit entity.⁸⁵ The public manufacturing model is a clear departure from the current pharmaceutical system, with a primary focus on patient and public health needs rather than profits.

The public sector is critical to pharmaceutical innovation. The US government is the largest single funder of basic and translational science in the world, with a budget of about \$39 billion in 2019.⁸⁶ In addition, numerous nonprofits support drug discovery and development.⁸⁷ But government and nonprofit investment has traditionally focused on early-stage investigations, with intellectual property often transferred to the private sector for later-stage clinical testing, and nearly always for production and dissemination of approved drug products. In leading conceptions, a public manufacturer would maintain control over drug

85. See Dan Liljenquist, Ge Bai & Gerard F. Anderson, *Addressing Generic-Drug Market Failures — The Case for Establishing a Nonprofit Manufacturer*, 378 NEW ENG. J. MED. 1857, 1858 (2018).

86. CONGRESSIONAL RESEARCH SERVICE, THE NATIONAL INSTITUTES OF HEALTH (NIH): BACKGROUND AND CONGRESSIONAL ISSUES 2 (Apr. 19, 2019), <https://crsreports.congress.gov/product/pdf/R/R41705> [<https://perma.cc/QPF4-EPL6>].

87. Rahul Nayak, Jerry Avorn & Aaron S. Kesselheim, *Public Sector Financial Support for Late Stage Discovery of New Drugs in the United States: Cohort Study*, 367 BMJ 1, 8 (2019).

development, testing, and production for widespread use, enabling the sale of medications at more affordable prices than could be expected of for-profit manufacturers. Such a model could help advance innovation in key areas of medical need that have been neglected or abandoned by the for-profit sector.⁸⁸ For example, in 2019, Amgen joined several other large pharmaceutical companies in reducing research and development investments in central nervous system drugs.⁸⁹

Public manufacturing has also been proposed in two production contexts: addressing market failures and drug shortages.⁹⁰ One example of a market at risk of failure is essential off-patent medicines supplied by small numbers of manufacturers. In such circumstances, due to the lack of competition, manufacturers have been able to increase prices, sometimes by shocking amounts. A highly publicized case of such price gouging was Turing Pharmaceuticals' over 5,000% markup of the antiparasitic drug pyrimethamine (Daraprim).⁹¹ Another example was Valeant Pharmaceuticals' price increase of penicillamine and trientine, treatments for a rare condition affecting the ability to process copper.⁹² These price hikes have made drugs prohibitively expensive for patients. Facilitating public manufacturing of such products would prevent pharmaceutical manufacturers like Turing and Valeant from cornering a market.⁹³ Overall, one-third or more of off-patent drugs may be supplied by three or fewer manufacturers and may be at risk for such market failures.⁹⁴

Generic drugs that are supplied by a limited set of manufacturers can also increase the risk of shortages. Recently, sterile intravenous medications used by hospitals—including sodium bicarbonate, injectable morphine, and sodium nitroprusside—suffered shortages in part due to natural disasters in Puerto Rico, a

88. Szymon Jarosławski & Mondher Toumi, *Non-profit Drug Research and Development: The Case Study of Genethon*, 7 J. OF MKT. ACCESS & HEALTH POL'Y 1, 1 (2018); Ameet Sarpatwari, Dana Brown & Aaron S. Kesselheim, *Development of a National Public Pharmaceutical Research and Development Institute*, 48 J. LAW, MED. & ETHICS 225, 225 (2020).

89. Andrew Dunn, *Amgen Exits Neuroscience R&D as Pharma Pulls Back from Field*, BIOPHARMA DIVE (Oct. 30, 2019), <https://www.biopharmadive.com/news/amgen-exits-neuroscience-rd-as-pharma-pulls-back-from-field/566157/> [<https://perma.cc/EV8C-Q96U>].

90. See Reed Abelson & Katie Thomas, *Fed Up With Drug Companies, Hospitals Decide to Start Their Own*, N.Y. TIMES (January 18, 2018), <https://www.nytimes.com/2018/01/18/health/drug-prices-hospitals.html> [<https://perma.cc/86HH-SC5M>].

91. Jing Luo, Ameet Sarpatwari & Aaron S. Kesselheim, *Regulatory Solutions to the Problem of High Generic Drug Costs*, 2(4) OPEN FORUM INFECTIOUS DISEASES 1, 1 (2015).

92. See Melody Petersen, *How 4 Drug Companies Rapidly Raises Prices on Life-Saving Drugs*, L.A. TIMES (December 21, 2016), <https://www.latimes.com/business/la-fi-senate-drug-price-study-20161221-story.html>.

93. See Liljenquist, Bai & Anderson, *supra* note 85, at 1859.

94. Ravi Gupta et al., *Generic Drug Approvals Since the 1984 Hatch-Waxman Act*, 176 JAMA INTERNAL MED. 1391, 1391 (Sept. 2016); see also Ernst, R. Berndt, Rena M. Conti & Stephen J. Murphy, *The Landscape of U.S. Prescription Drug Markets, 2004-2016*, NBER Working Paper # 23640 (2017), <https://www.nber.org/papers/w23640> [<https://perma.cc/66KF-NT6E>].

major manufacturing location for such products.⁹⁵ Public manufacturing can help address this issue by providing hospitals with a more diverse supply of needed medications. By relying on manufacturers that are not profit-incentivized, the risk of unexpected price spikes would be minimized.

Although promising, the public manufacturing model, faces several challenges. Commentators have highlighted concerns over financing, particularly given the high manufacturing costs of certain therapeutics, such as biologics,⁹⁶ and the possibility of private companies undermining public manufacturers by reducing the price of their products upon the approval of competing products.⁹⁷ Additionally, public manufacturers may lack the resources and expertise to launch, produce, and distribute drugs at an efficient scale. Critics of the public manufacturing model have suggested that this may compound problems with drug access, diverting resources to building new public organizations instead of supporting established pathways.⁹⁸ Finally, at least one review raised concerns that public manufacturing could have the unintended consequence of stifling innovation,⁹⁹ arguing that if a public entity were to market a product at a low price, it could undercut the potential revenue for new products, which could result in the abandonment of investigational products targeting the same disease or therapeutic area.

A. Characteristics of Public and Nonprofit Manufacturing Models

The public manufacturing model is a relatively new concept for drugs. The Affordable Drug Manufacturing Act, proposed by Senator Elizabeth Warren (D-MA) in 2018, was one of the first proposals in the US for a government authority to manufacture generic drugs (Table 3). Other nonprofit companies in the US and Europe have launched in recent years, devoted to transforming parts of the prescription drug market (Table 4).

1. Intended Purpose

Existing public manufacturers can be divided into two groups: those dedicated to innovative drug development and those to affordable generic supply. Genethon, the Institute for OneWorld Health, and the Institute for Pediatric Innovation are

95. Alison Kodjak, *Hospitals Prepare To Launch Their Own Drug Company To Fight High Prices And Shortages*, NPR (Sept. 6, 2018), <https://www.opb.org/news/article/npr-hospitals-prepare-to-launch-their-own-drug-company-to-fight-high-prices-and-shortages/> [https://perma.cc/6XKZ-YVE7].

96. Jarosławski & Toumi, *supra* note 88, at 3.

97. Liljenquist, Bai & Anderson, *supra* note 85, at 1857.

98. Szymon Jarosławski et al., *Non-Profit Drug Research and Development at a Crossroads*, 35 PHARMACEUTICAL RES. 1, 3 (2018).

99. Jarosławski & Toumi, *supra* note 88, at 3.

examples of nonprofit companies aimed at drug development in areas that have been neglected by the private sector. These nonprofits conduct similar activities as their private counterparts—including building in-house research teams, designing clinical trial protocols, managing research timelines, and guiding products through regulatory review—but have a public-oriented mission to provide their products close to marginal cost.¹⁰⁰

Other public manufacturers are dedicated to producing low-cost generic versions of drugs with expired patents. The most prominent example is Civica Rx, which launched in September 2018 as a nonprofit devoted to bringing stability to the hospital supply chain by manufacturing common generic drugs.¹⁰¹

2. Drug Criteria

Public manufacturers must decide which products to prioritize. Some nonprofits have a dedicated disease area upon formation, such as Genethon's focus on rare conditions or the Institute for OneWorld Health's focus on tropical diseases.¹⁰²

The nonprofit Civica Rx allows its hospital and health care system partners to prioritize which medications it manufactures. Its focus has been on stabilizing the pharmaceutical supply chain by supplying common hospital-administered generic drugs that have undergone price hikes or have drug shortages.¹⁰³ In October 2019, the nonprofit delivered its first manufactured drug, an injectable formulation of the antibiotic vancomycin, to a hospital facility in Utah.¹⁰⁴ Since then, Civica Rx has entered several partnerships with suppliers and health systems, including with Hikma Pharmaceuticals to provide 14 hospital drugs used in emergency care, surgery, pain, and hypertension;¹⁰⁵ with Thermo Fisher to develop nine drugs used

100. Victoria G. Hale, Katherine Woo & Helene Levens Lipton, *Oxymoron No More: The Potential of Nonprofit Drug Companies to Deliver on the Promise of Medicines for the Developing World*, 24(4) HEALTH AFF. 1057, 1059 (2005).

101. CIVICA RX, <https://civicarx.org/> [<https://perma.cc/28PD-8EV7>].

102. See GENETHON, <https://www.genethon.fr/en/> [<https://perma.cc/YW6T-RWVL>]; INSTITUTE FOR ONEWORLD HEALTH, <http://skoll.org/organization/institute-for-one-world-health/> [<https://perma.cc/X4XR-8FVM>].

103. Eric Palmer, *Hospital-backed Civica Rx Nabs Amgen Veteran as CEO and Targets 14 Drugs to Knock Off*, FIERCEPHARMA (Sept. 6, 2018), <https://www.fiercepharma.com/manufacturing/hospital-supported-civica-rx-to-produce-14-drugs-are-chronic-shortage> [<https://perma.cc/YR93-4HM8>].

104. Samantha Liss, *After Much Fanfare, Civica Rx Delivers Its 1st Drugs*, HEALTHCARE DIVE (Oct. 2, 2019), <https://www.healthcaredive.com/news/after-much-fanfare-civica-rx-delivers-its-1st-drugs/564189/> [<https://perma.cc/C7MN-3HG7>].

105. Press Release, PRNewswire, *Hikma and Civica Rx Sign Long-term Agreement to Reduce Generic Drug Shortages in the US* (July 23, 2019), <https://www.prnewswire.com/news-releases/hikma-and-civica-rx-sign-long-term-agreement-to-reduce-generic-drug-shortages-in-the-us-300889068.html> [<https://perma.cc/9V6Y-BNE6>] [hereinafter Hikma Press Release].

in critical or emergency care;¹⁰⁶ and with Blue Cross Blue Shield companies to create a new subsidiary devoted to lowering prices for high-cost generic drugs.¹⁰⁷

Proposals have called for government manufacturers to prioritize drugs with supply shortages or price hikes.¹⁰⁸ The Affordable Drug Manufacturing Act would establish an Office of Drug Manufacturing authorized to manufacture (or contract for the manufacture of) generic drugs under three listed conditions: that no company is manufacturing the drug; that fewer than three companies produce the drug and that the price has spiked or the drug is in shortage; or that fewer than three companies produce the drug, that the price is a barrier to patient access, and that the drug is listed as an “essential medicine” by the World Health Organization.¹⁰⁹

3. Manufacturing Control

Another variable in public manufacturing models is the degree of control public manufacturers exert over product development, production, and distribution. Given resource and expertise constraints, some nonprofits rely on outsourcing to contract organizations.¹¹⁰ For example, Civica Rx has stated that while its goal is to manufacture its own generic drugs, the company has initially relied on third-party manufacturers, such as Hikma Pharmaceuticals and Thermo Fisher,¹¹¹ while developing its own capabilities.¹¹²

Other nonprofit companies have chosen to sell their research programs to private developers. For example, the US Cystic Fibrosis Foundation developed a drug candidate and later sold it to a private company, which launched the product with a high annual price of \$300,000.¹¹³ Genethon also entered into exclusive licensing agreements with private biotechnology companies (e.g., AveXis, Spark Therapeutics) for several research programs.¹¹⁴ Although this model expedites

106. Jonathan Gardner, *Civica Advances Drug Supply Strategy with Thermo Fisher Deal*, BIOPHARMA DIVE (Jan. 16, 2020), <https://www.biopharmadive.com/news/civica-thermo-fisher-partner-drug-shortage-manufacturing/570617/> [<https://perma.cc/4PBN-NSW9>].

107. Press Release, Blue Cross Blue Shield Association, *Blue Cross and Blue Shield Companies Join Forces with Civica Rx to Lower Costs of Select High-Cost Generic Medications* (Jan. 22, 2020), <https://www.bcbs.com/press-releases/blue-cross-and-blue-shield-companies-join-forces-civica-rx-lower-costs-of-select> [<https://perma.cc/3PAE-3EBG>] [hereinafter Blue Cross Blue Shield Release].

108. Meredith Betz, *The New Nonprofit Pharmaceutical World: What's Up with That?*, NONPROFIT Q. (Sept. 12, 2018), <https://nonprofitquarterly.org/the-new-nonprofit-pharmaceutical-world-whats-up-with-that/> [<https://perma.cc/RZ8Y-2BYA>].

109. Affordable Drug Manufacturing Act, S.3775, 115th Cong. (2018) [hereinafter ADM Act].

110. Rena M. Conti, David O. Meltzer & Mark J Ratain, *Nonprofit Biomedical Companies*, 84(2) CLINICAL PHARMACOLOGY THERAPEUTICS 194, 197 (2008).

111. Hikma Press Release, *supra* note 105; Gardner, *supra* note 106.

112. Abelson & Thomas, *supra* note 90.

113. Jarosławski et al., *supra* note 98, at 2.

114. Jarosławski & Toumi, *supra* note 88, at 2.

clinical development, it also leads to ethical tensions. Commentators have noted that royalties returned to the nonprofit or government entity can be reinvested to support further research efforts. But while such reinvestment may be beneficial, high market prices limit patient access, which may be a core principle of the organization.¹¹⁵ This may be why Genethon has since announced its intentions to internalize its entire production chain, from discovery to manufacturing, enabling the organization to “fully recoup the public funds invested into research, and offer its products at affordable prices.”¹¹⁶ Such internalization is risky but can more reliably ensure fair market prices.

4. Governance

Public manufacturers should operate in ways that align with the core mission of promoting public health, which may require using different governance structures than private companies. Requiring philanthropic donors and major drug purchasers (e.g., hospital executives) to serve on the boards of nonprofit pharmaceutical companies would help ensure public accountability, given their financial interest in keeping drug prices low.¹¹⁷ Civica Rx’s Board of Advisors, for example, is comprised of several hospital directors, and their CEO is reportedly serving without compensation.¹¹⁸ By contrast, Harm Reduction Therapeutics, a nonprofit company devoted to developing a generic alternative to naloxone (Narcan), is led by a team comprised of former pharmaceutical executives¹¹⁹ and was primarily launched with a \$3.4 million grant from Purdue Pharma, a pharmaceutical company at the center of US growth in opioid sales.¹²⁰ This latter type of arrangement could lead to conflicts of interest, emphasizing the importance of transparency and autonomy.

5. Purchasing Agreements

One of the primary challenges facing public manufacturers is competing for market share with private companies that already have monopolies or broad market power. Private companies can use their control over distribution channels or market share to shut out competitors.¹²¹ These responses could be extreme enough

115. *See id.*

116. Jarosławski et al., *supra* note 98, at 3.

117. Liljenquist, Bai & Anderson, *supra* note 85, at 1858.

118. Marc Harrison, *How the Not-For-Profit Civica Rx Will Disrupt the Generic Drug Industry*, STAT (March 14, 2019), <https://www.statnews.com/2019/03/14/how-civica-rx-will-disrupt-generic-drug-industry/> [https://perma.cc/2MUF-SHK5].

119. HARM REDUCTION THERAPEUTICS, <https://www.harmreductiontherapeutics.org/> [https://perma.cc/3TR5-U8NC].

120. Betz, *supra* note 110.

121. Kodjak, *supra* note 95.

to spur antitrust action¹²² but can also be addressed with long-term purchasing contracts. Civica Rx developed a model to commit hospitals and other drug purchasers to contracts for the purchase of generics at pre-determined low prices.¹²³ An initial proposal suggested that purchasers would have to commit 50% of their annual purchases to Civica Rx at an established price for at least five years.¹²⁴ In January 2020, Blue Cross Blue Shield companies provided an initial \$55 million to create a Civica Rx subsidiary dedicated to developing generic drugs currently identified as high cost, with the first drugs expected to be available by 2022.¹²⁵

6. Intellectual Property

Questions remain about how public manufacturers should handle intellectual property, both their own and those held by other companies. Should public manufacturers seeking to develop novel products pursue patents, and if so, what should they do with them? Nonprofit and state-run entities could seek patents to protect their inventions from private companies but make the patents available through patent pools subject to “copyleft”-like licenses that ensure their free use.¹²⁶ Such pools collect patent rights across multiple patent holders, making them available to third parties through nonexclusive licenses. The first patent pool in the public health space was UNITAID’s Medicines Patent Pool established in 2010, which improved access to treatments for HIV, hepatitis C, and tuberculosis in low- and middle-income countries.¹²⁷ Patent pools, however, have been criticized for resulting in anticompetitive licensing practices or collusion among patent pool members.¹²⁸ To address this, public manufacturers should work with partners to ensure patent pool policies and rules are explicitly designed to encourage licensing and prevent fraud or abuse, thus facilitating uptake of licensed drug products.¹²⁹

122. See, e.g., Gianna Melillo, *NY Attorney General, Federal Trade Commission Sue Martin Shkreli*, AM. J. MANAGED CARE (Jan. 27, 2020), <https://www.ajmc.com/newsroom/ny-attorney-general-federal-trade-commission-sue-martin-shkreli> [<https://perma.cc/DTA3-U9SU>].

123. Betz, *supra* note 110.

124. Alex Kacik, *Civica Rx Aims to Stabilize Fragile Pharmaceutical Supply Chain*, 49(3) MOD. HEALTHCARE (Jan. 19, 2019), <https://www.modernhealthcare.com/article/20190119/NEWS/190119931/civica-rx-aims-to-stabilize-fragile-pharmaceutical-supply-chain> [<https://perma.cc/48YH-WLZD>].

125. Blue Cross Blue Shield Press Release, *supra* note 107.

126. See Sarpatwari, Brown & Kesselheim, *supra* note 88, at 226.

127. MEDICINES PATENT POOL, <https://medicinespatentpool.org/> [<https://perma.cc/BJY9-P5ZG>].

128. See, e.g., WORLD INTELLECTUAL PROPERTY ORGANIZATION, *Patent Pools and Antitrust – A Comparative Analysis* (March 2014), https://www.wipo.int/export/sites/www/ip-competition/en/studies/patent_pools_report.pdf [<https://perma.cc/YM24-4WSY>].

129. See David B. Resnik, *A Biotechnology Patent Pool: An Idea Whose Time Has Come?*, 3 J. PHIL. SCI. & L. 1, 13–14 (2003).

Public manufacturers dedicated to supplying generic drugs will likely need to focus on drugs with expired patents and regulatory exclusivities to avoid costly litigation over intellectual property controlled by private manufacturers. Another intellectual property strategy for nonprofits is to leverage the investment that private sector companies have already made by recycling off-patent drugs for novel indications or accepting patent donations from pharmaceutical companies.¹³⁰

7. *Funding Sources*

In its initial stages, nonprofit manufacturing may have to rely on philanthropic and charitable donations, in addition to advanced purchases from health care organizations.¹³¹ For example, the launch of Civica Rx was made possible by three philanthropic organizations (the Laura and John Arnold Foundation [now Arnold Ventures], the Peterson Center on Healthcare, and the Gary and Mary West Foundation) and advance donations from health care institutions.¹³² A government-run operation would likely require resources from health care budgets or other funding mechanisms, such as fees imposed on payers. The continued operation and manufacturing of drugs can be sustained by revenues from sales. The goal should be for the public manufacturer to become financially self-sufficient through its products.¹³³

B. *Outcomes from Public Manufacturing Models*

Given the limited number of nonprofit and government drug manufacturers, the empirical literature evaluating the effectiveness of public manufacturing models is sparse. However, case studies suggest that public manufacturing can beneficially supplement the current pharmaceutical system. The Civica Rx nonprofit is the leading example, with 18 medications in production, including vancomycin, diazepam, fentanyl, ketamine, ondansetron, midazolam, and naloxone,¹³⁴ and a substantial consumer base of more than 1,200 hospitals.¹³⁵

Nonprofit development companies have also experienced success. Genethon has produced several gene therapy programs that it has since licensed to biotechnology companies. With increasing dedication to internalize its operations, its primary sponsors established a firm called YoosKesi to help obtain regulatory approval for its products and ensure its independence, thus replacing the need for

130. Hale, Woo & Lipton, *supra* note 100, at 1059.

131. Liljenquist, Bai & Anderson, *supra* note 85, at 1858.

132. Kodjak, *supra* note 95.

133. Conti, Meltzer & Ratain, *supra* note 110, at 4.

134. *See id.*

135. CIVICA RX, <https://civicarx.org/> [<https://perma.cc/28PD-8EV7>].

a licensing partner in the private sector.¹³⁶ An adjacent example in the medical device space is the Alfred Mann Foundation, a nonprofit focused on developing technologies for movement disorders, diabetes, limb loss, and pain.¹³⁷ The Foundation's incubator program has resulted in a robust portfolio of new companies commercializing these technologies.¹³⁸ These examples show that drug development can be successfully accomplished at cost levels far below what is generally offered by the pharmaceutical industry.

The Affordable Drug Manufacturing Act was the first proposed federal legislation calling for a government manufacturer of generic products.¹³⁹ Since it did not emerge from committee when it was first introduced in 2018, it was re-introduced in January 2020 by Senator Elizabeth Warren in an amended version that specifically directs the government manufacture certain key products, like naloxone, insulin, and antibiotics.¹⁴⁰ The bill is designed to be a fix rather than a replacement for the pharmaceutical industry. However, critics have expressed concerns that a government agency overseen by the Department of Health and Human Services would have neither the resources nor expertise to manufacture cost-effective generic drugs in competition with established private generic manufacturers.¹⁴¹ Other commentators suggest that efforts should be spent on other solutions to fix issues in the generics market, including more rigorous antitrust legislation or streamlined approval pathways for generics.¹⁴² But with a growing number of crises related to generic drug availability and cost, government and nonprofit manufacturing may be a prudent solution.

C. Conclusions and Recommendations

As the number of public manufacturers continues to grow, data from these experiences are needed to gauge achievements and identify areas of improvement and how well they operate in conjunction with other policy and structural changes to the broader pharmaceutical system. Key inquiries to guide future development of these models include:

□ Aligning on outcome indicators (e.g., price, access) and methods of evaluation for performance-based assessments.

136. Jarosławski & Toumi, *supra* note 88, at 2.

137. ALFRED MANN FOUNDATION, <https://aemf.org/> [<https://perma.cc/3375-DGSN>].

138. *See id.*

139. ADM Act, *supra* note 109109.

140. Affordable Drug Manufacturing Act of 2020, S.3162, 116th Cong. (2020).

141. Avik Roy, *Should the Federal Government Manufacture Generic Drugs?*, FREOPP (Dec. 19, 2018), <https://freopp.org/should-the-federal-government-manufacture-generic-drugs-99520f3821d7> [<https://perma.cc/WNK3-BB6E>].

142. Mark Terry, *Point-Counterpoint: Senator Warren's Generic Drug Proposal*, BIOSPACE (Dec. 26, 2018), <https://www.biospace.com/article/senator-warren-proposes-government-manufacture-of-generic-drugs/> [<https://perma.cc/G6BH-WLG5>].

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□ Conducting qualitative surveys of payers and stakeholders in the pharmaceutical industry to better understand and predict private sector perspectives or reactions.

□ Modeling the viability of various manufacturing models (e.g., internalized processes vs. outsourcing) to ensure sustainability.

Public manufacturers will be distinctive in the current pharmaceutical market if they adhere to the mission of providing affordable and accessible drugs. This will require the appropriate governance, intellectual property, and incentive frameworks. Nonprofit and state-run entities must not turn into early-stage drug candidate developers for later investment by private sector companies. To protect against industry capture, governance of public manufacturing entities must be designed with clear objectives, transparency, and public participation in mind. The Democracy Collaborative proposal suggests creating public entities at the state or municipal level with two-tiered agency structures: one governing body and one operating body set up as a public trust.¹⁴³ This setup would provide public manufacturers insulation from political influence and create opportunities for public engagement. The proposal also recommends oversight boards comprised of different stakeholders (e.g., elected representatives, patient advocates) to ensure accountability. Public manufacturers must also maintain flexibility in their drug portfolio strategies to adapt to evolving patient and market needs. Finally, significant resources may need to be deployed for public manufacturing of increasingly complex drugs, including biologics.

TABLE 3: SELECTED PROPOSED PUBLIC MANUFACTURING MODELS

Proposal	Description
Affordable Drug Manufacturing Act 2020	Establishes an Office of Drug Manufacturing within the Department of Health and Human Services, charged with lowering prices, increasing competition, and addressing shortages in the market of prescription drugs. Authorizes the Office to manufacture or contract out the manufacture of generic drugs under certain conditions.

143. See Dana Brown, *Medicine for All: The Case for a Public Option in the Pharmaceutical Industry*, THE DEMOCRACY COLLABORATIVE (Sept. 2019), <https://thenextsystem.org/medicineforall> [<https://perma.cc/56D2-A6V4>].

Democracy Collaborative Proposal	Proposes a national public pharmaceutical research and development institute for full-cycle drug development with a commitment “to contributing to safe, adequate, and accessible supply of essential medicines in the US; to maximum transparency; and to management in the public interest.”
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TABLE 4: SELECTED IMPLEMENTED PUBLIC MANUFACTURING MODELS

Model	Description
Civica Rx	A nonprofit pharmaceutical company formed by a coalition of health care organizations that aims to manufacture hospital-administered generic drugs, specifically those in short supply. Funded by several philanthropic organizations and more than 800 US hospitals.
Genethon	A nonprofit research and development organization with mission to “design gene therapy products for rare diseases and to ensure their pre-clinical and clinical development in order to provide patients with access to these innovative treatments.” Historically, it has sought partnerships with biotechnology companies (e.g., AveXis, Bluebird Bio, Orchard Therapeutics) for clinical development and marketing of its products. Recently, it has increased focused on in-house production and distribution to maintain control over the sale of its products.
Harm Reduction Therapeutics	A nonprofit pharmaceutical company that aims to develop and manufacture a low-cost generic alternative for Narcan (naloxone). The nonprofit is primarily funded by a \$3.42 million grant by Purdue Pharma.
Institute for OneWorld Health	The first nonprofit pharmaceutical company in the US (now the drug development affiliate of PATH, a global health organization). Launched several successful drug development projects for diseases that included diarrheal disease, malaria, and visceral leishmaniasis.

III. THE PUBLIC-PRIVATE PARTNERSHIP MODEL

A public-private partnership (PPP) entails “a long-term contract between a private party and a [public entity], for providing a public asset or service, in which the private party bears significant risk and management responsibility.”¹⁴⁴ By combining the technical knowledge and management skills of private enterprise with the social accountability of public actors, PPPs are intended to serve as an efficient means of meeting societal needs.

As with all collaborations, a key challenge facing PPPs is achieving alignment between partnering parties.¹⁴⁵ Collaborators must agree on intended aims, timelines, and contractual terms, which can cause delay. For example, a survey of academic investigators found that contract negotiations were a primary barrier to collaboration with the pharmaceutical industry.¹⁴⁶

Another challenge is risk management. Information and resource asymmetries exist between organizations, which may lead to inappropriate distribution of risk among involved parties.¹⁴⁷ The suitable division of responsibilities and liabilities in a collaboration is particularly important for long-term research projects spanning multiple years or decades.

A. Characteristics of Public-Private Partnership Models

The number of biomedical PPPs has increased dramatically in recent years.¹⁴⁸ The leading US convener of such partnerships is the Biomedical Advanced Research and Development Authority (BARDA), a federal body created in 2006 to prepare society with biodefense and pandemic tools.¹⁴⁹ BARDA-organized PPPs have contributed to the development of more than 50 FDA-approved products addressing chemical, biological, radiological, and nuclear threats.¹⁵⁰ Around the

144. *Public-Private Partnerships – Reference Guide Version 1.0*, WORLD BANK INST. 1, 11 (2012).

145. Oktay Yildirim et al., *Opportunities and Challenges for Drug Development: Public-Private Partnerships, Adaptive Designs and Big Data*, 7 FRONTIERS IN PHARMACOLOGY 1, 5 (2016).

146. Marjan Amiri & Martin C. Michel, *Expectations and Satisfaction of Academic Investigators in Nonclinical Collaboration with the Pharmaceutical Industry*, 388 NAUNYN-SCHMIEDEBERG’S ARCH. PHARMACOLOGY 613, 613 (2015).

147. Jens K. Roehrich, Michael A. Lewis & Gerard George, *Are Public-Private Partnerships a Healthy Option? A Systematic Literature Review*, 113 SOC. SCI. & MED. 110, 114 (2014).

148. *See Build and Beyond: The (r)evolution of Healthcare PPPs*, PRICEWATERHOUSECOOPERS (2010), <https://www.pwc.se/sv/halso-sjukvard/assets/build-and-beyond-the-revolution-of-healthcare-ppps.pdf> [<https://perma.cc/6SVA-MMVY>].

149. BARDA STRATEGIC PLAN 2011 – 2016, BARDA (2011), <https://www.phe.gov/about/barda/Documents/barda-strategic-plan.pdf> [<https://perma.cc/75UB-TVAD>].

150. Kimberly Buckmon, *The Power of Partnership: BARDA Ushers in 50th FDA-Approved Product for Health Security*, ASPR BLOG (Oct. 10, 2019),

same time BARDA was established, various nonprofit organizations formed PPPs to spur research and development efforts for select diseases, especially those disproportionately affecting developing countries.¹⁵¹ These PPPs differ in scope, duration, and structure but all share a common goal of efficient drug development by relying on a bidirectional exchange of resources and expertise.¹⁵²

1. Participants

PPPs are formed by partnerships spanning three sectors: government, industry, and civil society.¹⁵³ PPPs often originate from the government, including the Medicines for Malaria Venture, which launched with funding from several European countries.¹⁵⁴ However, civil society organizations also play a critical role, given their awareness of unmet needs and access to patient networks. For example, the Drugs for Neglected Diseases Initiative (DNDi), originated from a working group organized by the nonprofit Médecins Sans Frontières.¹⁵⁵

2. Scope

Some PPPs are simple collaborations between one company and a specific group of researchers. Others involve strategic alliances between one company and an entire academic institution.¹⁵⁶ A few are expansive multi-stakeholder consortia involving numerous organizations spanning multiple sectors. For example, with an annual budget of more than €5 billion, the Innovative Medicines Initiative (IMI) oversees several smaller consortia that have distinct missions and fields more than 120 projects (Table 5).¹⁵⁷

<https://www.phe.gov/ASPRBlog/Lists/Posts/Post.aspx?ID=362> [<https://perma.cc/W7AP-53F5>].

151. Chan Harjivan & George Dougherty, *Drug Development for Government, Nonprofit, and Developing-World Markets*, 7 PHARMACEUTICAL TECH. SOURCING AND MGMT. (2011).

152. Importantly, some programs may fall under both the public manufacturing and PPP models. For example, Drugs for Neglected Diseases initiative (DNDi) is a nonprofit manufacturer (i.e., public manufacturing model) that engages in public-private partnerships (i.e., PPP model) to develop treatments.

153. Remco L. A. de Vruhe & Daan J. A. Crommelin, *Reflections on the Future of Pharmaceutical Public-Private Partnerships: From Input to Impact*, 34 PHARMACEUTICAL RES. 1985, 1990 (2017).

154. DRUGS FOR NEGLECTED DISEASES INITIATIVE, <https://www.dndi.org/> [<https://perma.cc/4TLF-YV8F>]; MEDICINES FOR MALARIA VENTURE, <https://www.mmv.org/> [<https://perma.cc/S9VW-MV4W>].

155. *History*, DRUGS FOR NEGLECTED DISEASES INITIATIVE, <https://www.dndi.org/about-dndi/history/> [<https://perma.cc/V6BV-CQ7R>].

156. Yildirim et al., *supra* note 145, at 4.

157. Elisabetta Vaudano, *The Innovative Medicines Initiative: A Public Private Partnership Model to Foster Drug Discovery*, 6 COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY J. (2013); Matthias Gottwald et al., *Public-Private Partnerships in Lead Discovery: Overview and Case Studies*, 349(9) ARCHIV DER PHARMAZIE 692, 695 (2016).

3. *Intended Purpose*

There are three broad categories of biomedical PPPs: access PPPs, precompetitive PPPs, and product development PPPs.¹⁵⁸ Access PPPs focus on promoting availability of drugs in developing countries, typically by overcoming obstacles in distribution systems.¹⁵⁹

Precompetitive PPPs generate foundational scientific concepts and infrastructure to advance drug development. They aim to reduce the risk of late-stage development failures, resulting in outputs such as research tools, platform technologies, shared databases, and predictive models. As their name implies, precompetitive PPPs do not directly compete with pharmaceutical companies, but rather supply insights that pharmaceutical manufacturers would take up in developing their own products.¹⁶⁰

The IMI consortia are one prominent example of precompetitive PPPs. Their research goals are proposed by pharmaceutical companies, which helps ensure that projects will have an impact on the industry.¹⁶¹ The output of these consortia can be grouped into five broad categories: validated models for drug development, approaches to predict adverse drug effects, compiled data from various sources for novel analysis, standards for drug development, and approaches for more efficient patient enrollment in clinical trials.¹⁶² Other consortia dedicated to specific disease areas, such as diabetes (SUMMIT) or severe asthma (U-BIOPRED), are limited to precompetitive efforts like biomarker identification and disease understanding.

Finally, product development PPPs identify and guide specific drug candidates through clinical trials for eventual regulatory approval and market launch.¹⁶³ Government and nonprofit institutions are motivated to participate in these PPPs because they gain the opportunity to “set the directions for innovation aimed at key public health milestones,”¹⁶⁴ while private sector innovators benefit from access to foundational research and relationships with key experts.

158. Roy Widdus, *Public-Private Partnerships: An Overview*, 99 *TRANSACTIONS ROYAL SOCIETY TROPICAL MED. & HYGIENE* S1, S5 (2005).

159. de Vruet & Crommelin, *supra* note 153, at 1987.

160. Gottwald et al., *supra* note 157, at 694.

161. *Id.* at 693.

162. Hugh Laverty, Magda Gunn & Michel Goldman, *Improving R&D Productivity of Pharmaceutical Companies Through Public-Private Partnership: Experiences from the Innovative Medicines Initiative*, 12 *EXPERT REV. PHARMACOECONOMICS & OUTCOMES RES.* 545, 546 (2012).

163. Widdus, *supra* note 158, at S5.

164. Mariana Mazzucato et al., *The People's Prescription: Re-imagining Health Innovation to Deliver Public Value*, UCL INST. FOR INNOVATION AND PUB. PURPOSE 1, 7 (2018).

4. Intellectual Property

Intellectual property frameworks associated with PPPs affect downstream product marketing and access. Stevens et al. distinguished three such frameworks: partnership-focused, open collaboration, and hybrid.¹⁶⁵ In partnership-focused frameworks, rights to new knowledge and technology arising from PPPs (“foreground intellectual property”) are carefully negotiated among the various partners. Such frameworks are typically used in product development PPPs, for which intellectual property ownership of the final product is highly important. By contrast, open collaboration frameworks allow data sharing in the public domain. In the middle are hybrid frameworks, which are tailored to individual PPPs, but generally limit only some foreground intellectual property rights.

Precompetitive PPPs often employ open collaboration frameworks. For example, the Structural Genomics Consortium requires all results be placed in a public domain without restriction,¹⁶⁶ while the Alzheimer’s Disease Neuroimaging Initiative hosts its research on an open database, which has been cited by 750 publications.¹⁶⁷ Yet despite the open collaborative framework of many IMI consortia, several academic partners have criticized IMI for intellectual property policies that favor the private sector’s financial interests.¹⁶⁸ Academic partners have specifically decried ambiguous intellectual property policies that allow pharmaceutical industry partners to exploit technology developed as part of a research project, without having to obtain consent from other consortium partners.¹⁶⁹ Intellectual property frameworks and policies are therefore important to determine clearly upfront during the formation of PPPs to ensure transparency and trust among partners.

5. Relationship with Regulatory Authorities

Many PPPs have been set up to communicate with regulatory authorities in the early stages of drug candidate development. These PPPs can serve as knowledge platforms that allow regulatory authorities to better understand not only new disease evaluation tools, but also academic and industry stakeholder

165. Hilde Stevens et al., *Intellectual Property Policies in Early-Phase Research in Public-Private Partnerships*, 34 NATURE BIOTECHNOLOGY 504 (2016).

166. Gottwald et al., *supra* note 158, at 694.

167. Michael W. Weiner et al., *The Alzheimer’s Disease Neuroimaging Initiative: A Review of Papers Published Since Its Inception*, 9 ALZHEIMER’S & DEMENTIA e111 (2013).

168. Gunjan Sinha, *Spat Over IMI Funding and Intellectual Property*, 29 NATURE BIOTECHNOLOGY 473, 473 (2011).

169. *See id.* (quoting Michael Browne, Head of European Research and Development at University College, London: “The wording of the IP policy is ambiguous” such that academic institutions “get short shrift from both ends.”).

perspectives.¹⁷⁰ One prominent example is the Critical Path Initiative, which the FDA launched in 2004 to create new evaluation tools and standards for clinical trials. The Critical Path Initiative has since formed several consortia, including the Predictive Safety Testing Consortium (identifying safety biomarkers), Patient-Reported Outcome Consortium (evaluating patient-reported outcome instruments), and the Critical Path for Alzheimer’s Disease (improving development process for treatments of neurodegenerative disorders), which have contributed to changing regulatory approaches and frameworks related to these diseases and concepts.¹⁷¹

6. Funding Sources

Funding sources for PPPs include grants, fees from participating member organizations, and donations from private foundations. Contributions are often split among partners. For example, 50% of research funding for the Netherlands’ Technology Top Institute comes from the government and 25% each from public and private partners.¹⁷²

B. Outcomes from Public-Private Partnership Models

Comparative outcome assessments for PPPs are difficult to conduct as PPPs differ widely in purpose, number of participants, and financial budgets. Furthermore, appropriate outcome indicators are not well-established in the literature. A previous study revealed that only 2 out of a total of 12 suggested indicators of outcome for PPPs were considered measurable by experts.¹⁷³

A value assessment framework by de Vruh et al. suggested classifying outcome indicators for biomedical PPPs into five categories: networks and collaboration, research activity and knowledge, knowledge sharing and dissemination, human capital, and financials and operations.¹⁷⁴ This framework was applied to analyze four PPPs of varying size, location, and research focus: the Structural Genomics Consortium, the Alzheimer’s Disease Neuroimaging Initiative, the Top Institute Pharma, and the IMI. The investigators concluded that the review “provide[s] clear evidence that precompetitive biomedical PPPs have

170. Michel Goldman, Carolyn Compton & Barbara B Mittleman, *Public-Private Partnerships as Driving Forces in the Quest for Innovative Medicines*, 2 CLINICAL AND TRANSLATIONAL MED. 1, 2 (2013).

171. Janet Woodcock & Raymond Woolsey, *The FDA Critical Path Initiative and Its Influence on New Drug Development*, 59 ANN. REV. OF MED. 1 (2008).

172. Peter R. Luijten et al., *Public-Private Partnerships in Translational Medicine: Concepts and Practical Examples*, 161 J. CONTROLLED RELEASE 416, 417 (2012).

173. Koen Dittrich, *How Valuable is Your Partnership? A Framework for Valuing Public-Private Research Partnerships in Biomedical Sciences*, DRUID SOCIETY MEETINGS 1, 23 (2012).

174. de Vruh & Crommelin, *supra* note 153, at 1990–91.

started to generate tangible outcomes.”¹⁷⁵ However, the study acknowledged that “multi-indicator, multi-method” approaches involving quantitative and qualitative analyses would be necessary in future evaluations of PPPs given the complex interactions between multiple stakeholders.¹⁷⁶

In 2016, the IMI appointed an expert group to conduct a socio-economic impact assessment of nine IMI consortia.¹⁷⁷ The group created an impact assessment model “to capture the complexities of actual practice but remain simple enough to be useful for empirical analysis and clarification of observed phenomena.”¹⁷⁸ This model involved three steps. First, the position of the PPP in the innovation system was identified (e.g., preclinical research, training, clinical development). Second, quantitative mediators and intermediate outcomes were characterized, including number of scientific publications, patents, licenses, databases, products, and trained personnel. Finally, socio-economic impact was assessed based on factors such as development time and costs, health benefits, new businesses, sales, and employment. The report summarized quantitative outputs for several ongoing IMI projects, highlighting the areas in which socio-economic impact had not yet been realized. The advantage of IMI’s impact assessment model is its ability to compare quantitative outputs and socio-economic factors at various stages of implementation. A similar impact assessment applied to PPPs outside of IMI consortia, including initiatives such as BARDA and the Critical Path Initiative, is needed.

Select PPPs have been successful in developing and commercializing novel treatments. For example, since 2003, DNDi has spearheaded the development of 7 new treatments targeted at various neglected diseases, including malaria, Chagas disease, leishmaniasis, and pediatric HIV.¹⁷⁹ The organization expects to develop 16 to 18 new treatments by 2023.¹⁸⁰

However, a common criticism of PPPs is they often lack safeguards to ensure reasonable pricing of the products they produce. For example, a BARDA program came under scrutiny for transferring a license to its Zika vaccine to Sanofi without affordable access conditions.¹⁸¹ BARDA subsequently partnered with Takeda

175. *See id.* at 1995.

176. *See id.* at 1992.

177. IMI SOCIO-ECONOMIC IMPACT ASSESSMENT EXPERT GROUP FINAL REPORT, INNOVATIVE MED. INITIATIVE 1 (May 2016), https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/SocioeconomicImpactAssessment_FINALMay2016.pdf [<https://perma.cc/R4EN-AU8F>].

178. *Id.* at 18.

179. *DNDi Achievements*, <https://www.dndi.org/achievements/> [<https://perma.cc/BAJ3-VTK2>].

180. *See id.*

181. Eric Sagonowsky, *U.S. Army Can’t Add A Pricing Safeguard to Sanofi’s Zika Vaccine License, Official Says*, FIERCEPHARMA (Apr. 25, 2017), <https://www.fiercepharma.com/vaccines/u-s-army-can-t-add-pricing-safeguard-to-sanofi-zika-license-official-says> [<https://perma.cc/GF8R->

Pharmaceutical, awarding the company an initial contract of \$19.8 million for Zika vaccine development through phase I testing and potential funding up to \$312 million for later-stage development,¹⁸² again without price guarantees. Control of drug pricing and marketing has often rested with the private partner due to the public entity's inability or unwillingness to implement or enforce an affordable price. Some public authorities have stated that exclusive licenses—absent price controls—are necessary for industry partners to invest in commercializing federally developed drugs.¹⁸³

C. Conclusions and Recommendations

Of the three PPP models discussed in this review, precompetitive PPPs are the most prevalent and most studied. As the number of PPPs continue to grow, additional research is needed to understand their successes and failures as well as steps in the drug development process in which they could play a greater role. Next steps should include:

- Identifying “bottleneck” areas of drug development or other issue areas best targeted by PPP models.
- Establishing broad consensus on output indicators to assess and track research project achievements and failures.
- Exploring various IP frameworks to implement in PPP contracts to ensure increased access to drugs upon successful development.

Early collaboration between private and public stakeholders has a positive influence in shaping the direction of drug development. PPPs are a proven method to facilitate this collaboration, having resulted in significant innovation. However, most PPPs continue to operate within the existing system that allows private pharmaceutical companies to retain patent-based monopolies, which can lead to high prices and suboptimal access. Reforms related to intellectual property rights associated with PPP models are necessary to prevent this outcome. Specifically, exclusive licenses granted to private partners should be discouraged. Any such licenses that are executed should include provisions designed to safeguard public interest, such as price controls, limits to the scope of exclusivity, or reductions to the years of exclusivity.

TABLE 5: SELECTED IMPLEMENTED PUBLIC-PRIVATE PARTNERSHIP MODELS

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182. Press Release, Takeda, *Takeda to Develop Zika Vaccine with up to \$312 Million in Funding from US Government* (Sept. 2, 2016), [https://www.takeda.com/newsroom/newsreleases/2016/Takeda-to-develop-Zika-Vaccine-with-up-to-\\$312-million/](https://www.takeda.com/newsroom/newsreleases/2016/Takeda-to-develop-Zika-Vaccine-with-up-to-$312-million/) [<https://perma.cc/6LLO-W55K>].

183. See, e.g., Sagonowsky, *supra* note 181.

Model	Description
Alzheimer’s Disease Neuroimaging Initiative (ADNI)	A collaboration between leading Alzheimer research centers, the National Institute on Aging, 13 pharmaceutical companies, and nonprofit foundations to identify, validate, and standardize disease biomarkers for use in clinical trials. Its core project is a multi-site, longitudinal clinical study tracking cognitive impairment and early Alzheimer’s Disease. More than 750 publications have cited use of ADNI data.
Biomedical Advanced Research and Development Authority (BARDA)	The office within Department of Human and Health Services that procures and develops medical countermeasures against health threats to the US population. Partners with private biopharmaceutical companies to develop and stockpile vaccines and treatments for public health emergencies. Between 2007 and 2017, BARDA stockpiled 21 products and invested more than \$2.5 billion in advanced research and development of medical countermeasures.
Critical Path Initiative (CPI)	An independent organization focused on reducing the time, cost, and risk of drug development and regulatory review. Formed several PPP consortia under its umbrella, including the Predictive Safety Testing Consortium (identifying safety biomarkers), Patient-Reported Outcome Consortium (evaluating patient-reported outcome instruments), and the Critical Path for Alzheimer's Disease (improving development process for treatments of neurodegenerative disorders).
Drugs for Neglected Diseases Initiative (DNDi)	A public-private partnership established to develop drugs for disease neglected by industry, including sleeping sickness, Chagas disease, leishmaniasis, filaria, and later pediatric HIV/AIDS. The partnership relies on 50% public and 50% private contributions to fund research and development, has developed six new treatments since its inception, and expects to develop 10 to 12 additional new treatments by 2023.

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eTOX	An IMI consortium of 13 pharmaceutical companies, 11 academic or nonprofit organizations, and 6 small and mid-sized enterprises dedicated to advancing predictive models of <i>in vivo</i> toxicology of novel drugs. The consortium created the largest database of preclinical safety data, with access to more than 7,000 systemic toxicity data sets corresponding to more than 1,800 compounds.
European Lead Factory (ELF)	An IMI consortium of 7 European companies, 13 public companies, and 10 small and mid-sized enterprises aimed at creating a pooled, diverse library of 500,000 compounds linked to a central screening center to identify novel targets.
Innovative Medicines Initiative (IMI)	A multi-consortia collaboration between the European pharmaceutical industry and the European Commission that implements and coordinates projects aimed at developing new tools and methods for drug development and improving data management. IMI projects have collectively identified over 460 biomarker candidates and over 20 new drug targets, in addition to developing over 50 animal models, over 100 <i>in vitro</i> models, and over 100 <i>in silico</i> models.
Innovative Medicines Initiative for Diabetes (IMIDIA)	An IMI consortium aimed at improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes. The consortium generated and commercially developed the first fully functional human beta cell line suitable for drug research, now used by pharmaceutical companies developing antidiabetic therapeutics.
Kinetics for Drug Discovery (K4DD)	An IMI consortium of 7 pharmaceutical companies, 9 public partners, and 4 small- and moderate-sized entities to enable the adoption of drug-target binding kinetics analysis in the drug discovery process and to improve prediction of binding kinetics to drug effect. Data generated by the consortium are integrated into a publicly accessible database.

Medicines for Malaria Venture (MMV)	A drug development venture devoted to discovery, development, and distribution of new antimalarial drugs. Partnering pharmaceutical companies include GlaxoSmithKline (to identify new drug leads) and Ranbaxy (to guide an antimalaria candidate through clinical trials).
NEWMEDS	An IMI consortium focused on developing new animal models that use brain recording and behavioral tests to identify innovative and effective drugs for schizophrenia. The consortium evaluated the impact of copy number variations conferring risk of schizophrenia by phenotyping more than 1,300 subjects carrying certain mutations.
SAFE-T	An IMI consortium creating sensitive and specific tests to diagnose and monitor drug-induced injury to the kidney, liver, and vascular systems. The consortium evaluated 153 potential translatable biomarker candidates for monitoring drug-induced injury.
Structural Genomics Consortium (SGC)	An IMI consortium of nonprofit researchers in collaboration with industry partners, focused on advancing structural biology. The consortium is committed to placing all data and research information into the public domain without restrictions and has published more than 2,000 novel protein structures and 40 chemical probes.
SUMMIT	An IMI consortium aimed at developing new biomarkers, imaging techniques, and animal models to advance drug development in diabetes. The consortium generated the largest GWAS data collection of over 26,000 cases of Type 1 and 2 diabetic nephropathy in addition to cardiovascular disease.
Top Institute Pharma (TI Pharma)	A public-private partnership aimed at building pharmaceutical research and development networks in five disease areas (autoimmune diseases, cardiovascular disease, cancer, infectious disease, and brain diseases). The partnership has resulted in 470 trained PhD and postdoctoral fellows, 750 publications, 41 lead compounds, 18 novel formulations, 11 biomarkers, 33 preclinical

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	models, 28 clinical models, 11 research databases, and 87 research tools.
U-BIOPRED	An IMI consortium aimed at using information and samples from adults and children with severe asthma to understand more about the disease to aid in drug development. The consortium recruited a large clinical cohort of severe asthma patients: 1,025 adult and pediatric subjects were assessed at 14 clinical centers across Europe.

CONCLUSION

While lucrative to manufacturers, the current pharmaceutical innovation system does not incentivize the development of drugs of greatest patient or public health need and has led to pricing that patients and health care systems cannot afford. Delinkage, public manufacturing, and PPPs have been proposed as alternative models to address these shortcomings. Each model exhibits promise and can be meaningfully advanced in the short-term in several ways. For example, economic modeling of prize sizes necessary to induce manufacturers and of the budgetary impact of such prizes could convince government payers to fund delinkage pilots in discrete areas of market failure. Critical appraisal of the outcomes of existing public manufacturing models could inform their optimization and possible expansion. Finally, changes to intellectual property frameworks governing current product development PPPs could increase patient access to therapies emerging from such schemes. Timely investment in the resources necessary to perform such steps would likely reap large dividends.