2 Public–Private Partnerships as Models for New Drug Research and Development: The Future as Now

Frederick M. Abbott

I Introduction and Background

The international community is searching for ways to improve the system under which new pharmaceutical treatments, vaccines, and diagnostics are discovered, developed, and distributed. The predominant model relying on patents and regulatory market exclusivity, combined with pricing power, is creating enormous public and private budgetary pressures, and at least arguably is misallocating research and development (R&D) resources. The monolithic vertically integrated pharmaceutical originator is largely a myth. The drug discovery, development, and distribution process has long involved a wide range of participatory arrangements, with basic discovery, follow-on research, translation, and manufacturing technology functions distributed across in-house and external actors. A main distinguishing characteristic of the pharma originator company is its profit-driven motivation, as compared with alternative models such as public–private partnerships (PPPs) and product development partnerships (PDPs) that are motivated in other ways. Each of these models already has a substantial public or nonprofit financing component.

The question explored in this contribution is whether and how PPPs and PDPs should become a more significant part of the global pharmaceutical development and distribution system. The chapter begins by describing the current model of pharmaceutical R&D, including the blurry boundary between public and private R&D. Following this is a section surveying some current PPP and/or PDP models of R&D, and analyzing the advantages and limitations of PPPs and/or PDPs. The next part connects the R&D activities of these partnerships to capital markets and investment incentives in the R&D of public goods. This part of the chapter discusses the potential role of PPPs and/or PDPs as part of a delinkage of R&D from production and distribution functions. The chapter concludes that further experimentation with PPPs and PDPs is warranted.

II The Current Model of Pharmaceutical R&D

The world biomedical industry is generating innovative medical treatments. Much of this progress is based on the general advance of science. New research tools improve the capability of scientists to identify the causes of disease. As our understanding of biotechnological processes improves, so does the ability of researchers to create new types of intervention.

A vast "originator" industry,[1] chemical and biological, serves to channel capital toward potentially profitable pharmaceutical innovations. Key decisions are made by or through investment bankers.[2] Potential breakthroughs in treatment rely on a capital markets based pharmaceutical R&D framework to drive science forward. This predominant capital markets approach to innovation has drawbacks. Three are noteworthy: (1) the demand of capital markets for high rates of return impels originator (and also generic) companies to maximize profits, including by charging the highest possible price for drugs;[3] (2) the substantial premium on marketing and selling treatments demanded because profits depend on sales; and (3) the absence of attention to diseases or conditions for which there is a limited capacity to pay, which attract less investment in innovation because of limited prospect for profits.[4]

The originator industry and its drive for profits has been a long-standing target for criticism from public health-oriented groups. Nonetheless, the major originator pharmaceutical companies (pharma or pharma companies) do more than pay substantial salaries to officers and directors, distribute dividends, and repurchase shares. They support a complex infrastructure of universities, teaching hospitals, doctors, and researchers through contract and acquisition of technologies. The wealth generated by the pharma companies supports a network that provides much of the scientific backbone supporting and ultimately discovering new products. And it is worth noting that the major pharma companies are mainly owned by individuals through retirement, pension, and insurance plans, even if sometimes indirectly.[5] Wealthy hedge fund managers may benefit from increased shareholder value, but they own only a minor portion of these companies. These characteristics are important to consider in assessing the benefits and costs of the dominant capital markets driven model of R&D, and this chapter will revisit them in connection with alternative R&D models.

A *PPPs and PDPs Defined*

The terminology "public–private partnership" (PPP) and "product development partnership" (PDP) encompasses an extensive range of potential configurations. Their relationship to the profit-driven model described in the previous section has not been explored thoroughly. PPP suggests an institutional arrangement involving public funding, which is

[1] The term "originator" is customarily used to refer to the party that first obtains approval from the drug regulatory authority for the commercial marketing of a new drug.

[2] *See, e.g.*, Staff of S. Comm. on Fin., 114th Cong., The Price of Sovaldi and its Impact on the U.S. Health Care System, 106–10 (Comm. Print 2015).

[3] *See, generally*, Frederick M. Abbott, *Excessive Pharmaceutical Prices and Competition Law: Doctrinal Development to Protect Public Health*, 6 U.C. Irvine L. Rev. 281 (2016).

[4] *See, e.g.*, World Health Organization [WHO] – Special Programme for Res. and Training on Tropical Diseases [TDR], Health product research and development fund: a proposal for financing and operation, at, e.g., vii, 1 (2016); Bernard Pecoul et al., *Drugs for Neglected Diseases initiative [DNDi]*, U.N. High-Level Panel On Access to Meds. (Feb. 27, 2016), www.unsgaccessmeds.org/inbox/2016/2/27/bernard-pecoul.

[5] *See, e.g.*, Sam Ro, *Here's Who Owns the Stock Market*, Bus. Insider, Mar. 13, 2013, www.businessinsider.com/chart-stock-market-ownership-2013-3.

typically associated with governments. But most self-described PPPs in the biomedical area secure a significant portion of their funding from nongovernmental organizations, including foundations.[6] While the latter may be nonprofit and/or charitable organizations, they are neither public in the traditional sense of being responsible to an electorate or other political institution, nor are they private in the sense of profit-seeking enterprises.

PDP could refer to almost any R&D effort involving more than one entity (i.e., a partnership). There is nothing in the term that suggests governmental or NGO participation, as such. In the common parlance, the terms PPP and PDP tend to be used interchangeably, although an R&D enterprise involving two private pharma companies is unlikely to be referred to as a PPP but rather as simply a partnership involving collaborative R&D.

B *Public versus Private R&D*

A key issue in thinking about alternative mechanisms for innovation is whether government-owned and/or -operated R&D would be as successful – or better – in generating outcomes than the private sector. From an historical standpoint, evidence cuts both ways. Many important innovations have resulted from government-funded research programs and, likewise, many important innovations have been generated by individuals and enterprises working largely without government support.[7] Both government and private sector institutions have their advantages and disadvantages. Government organizations provide incentives in terms of legitimacy and status; private sector organizations provide incentives in terms of power and financial resources.[8] Performance in government and private sector institutions is typically benchmarked or assessed by different types of criteria. Both types of organization are capable of generating successful outcomes. Both types of organization are subject to institutional failure.

In this regard, combining public and private approaches to new drug R&D may have advantages and disadvantages depending upon the specific organizational arrangement, the target that is addressed, and ultimately the management of the enterprise. It seems doubtful that a particular organizational structure can be identified that would optimize the outcome in all cases.[9] Instead, perhaps, it is important to maintain open-mindedness about how particular R&D enterprises should be structured, and not rigidly insist on one institutional approach.

[6] *See infra* text accompanying notes 15–27.

[7] *See, e.g.*, Fred Block & Matthew R. Keller, *Where Do Innovations Come From? Transformations in the U.S. National Innovation System, 1970–2006*, The Info. Tech. & Innovation Found. [ITIF] (Jul. 9, 2008), www.itif.org/files/Where_do_innovations_come_from.pdf. For earlier references regarding the sources of innovation, see Frederick M. Abbott, *Protecting First World Assets in the Third World: Intellectual Property Negotiations in the GATT Multilateral Framework*, 22 Vand. J. Transnat'l L. 689, 697–700 (1989).

[8] For a discussion of this framework perspective, see Harold Lasswell & Abraham Kaplan, Power and Society: A Framework for Political Inquiry (Yale University Press 1950; New Haven Press (as assignee)).

[9] *Accord*, Block & Keller, supra note 7. *See also* Ashish Arora, Wesley M. Cohen, & John P. Walsh, *The Acquisition and Commercialization of Invention in American Manufacturing: Incidence and Impact*, 45 Res. Pol'y 1113 (2016), www.nber.org/papers/w20264.

C *The Blurry Boundary Between Public and Private R&D*

As a factual matter, virtually all (if not all) enterprises developing pharmaceutical products (including small molecule, biologic, vaccines, and diagnostics) involve a combination of public and private funding. The mix is a matter of degree. For example, the development of a new drug by a large originator company based in the United States (US) commonly involves early-stage research conducted or funded by the National Institutes of Health (NIH), and possibly the patenting of technology under the terms of the Bayh-Dole Act.[10] If not within the NIH itself, some part of the R&D effort will almost certainly have been conducted at a university or teaching hospital, each of which would almost certainly have been supported by some public/government funding. There may from time to time be an exception where a private entity develops a new drug product wholly on its own initiative without any direct government support. But even in such case, the R&D would generate tax credits or deductions against income, another form of government support, and private sector companies generally depend on government institutions to provide the overall legal framework in which they can and do function.

A government insulates the originator from competition by copyists through the grant of patents and marketing exclusivity; it also provides considerable regulatory infrastructure support through the activities of the drug regulatory authorities, customs authorities, and so on. Originator companies raise funds through securities markets that are also supported in various ways by government insurance and regulation.

Incentives are often characterized as "push" or "pull." The former refers to subsidization or grant funding that pays for R&D up front, and the latter refers to advance offtake or procurement agreements that guarantee a return on the successful completion of R&D. When referring to nontraditional R&D models such as PPPs and PDPs, the practice of negotiating advance commitments is not uncommon as a means of providing security to up-front funding entities (i.e., a combination of push and pull).[11] As a practical matter, most R&D efforts undertaken by originator pharma companies also rely on publicly-funded offtake agreements as pull incentives.[12] For example, in the United States, the Veterans Administration, Medicare, and Medicaid programs provide a stable source of procurement or offtake for new drugs developed by the originator industry.[13] In fiscal

[10] *See, e.g.*, Frederick M. Abbott & Graham Dukes, Global Pharmaceutical Policy 16–85 (2009).

[11] For definitions, see Report of the United Nations Secretary General's High Level Panel on Access to Medicines 29 (2016).

[12] If a new drug has been approved by the FDA, it may be subject to some comparative efficacy assessment by governmental procurement authorities. In most cases a new drug will be added to one or more formularies, federal or state.

[13] According to Avelere Health, *Federal Spending on Brand Pharmaceuticals* (2015):

> "Health Federal Spending on Outpatient Prescription Drugs for Medicare and Medicaid in 2014
> Based on data from the Medicare Trustees Report, the National Health Expenditures (NHE) Accounts, the Centers for Medicare & Medicaid Services (CMS), and other sources, the federal government spent an estimated $127 billion on outpatient prescription drugs covered by Medicare, Medicaid, VA, and TRICARE in calendar year 2014:
>
> - Medicaid: $15 billion
> - Medicare Part D: $81 billion
> - Medicare Part B: $22 billion
> - VA: $3 billion
> - TRICARE: $5 billion" (at pg. 5)

year 2016, prescription drug spending in the United States amounted to $328.6 billion,[14] and at least half of that can be accounted for by government spending (federal and state combined).[15] Even in the traditional sense of originator new drug development, there is a major pull incentive in the form of budgeted government procurement expenditure.

The border or boundary line between private and public drug development is blurry and ever-shifting. It is different depending on the country where activities are taking place. Categorical distinction between public and private pharmaceutical development is mainly a fiction.

III Current PPP and/or PDP Models of R&D

As noted previously, virtually all new drug development can be characterized as involving a combination of public and private funding. One potential distinction between predominantly private sector enterprises and the institutions typically referred to as PPPs and PDPs is that the latter typically provide their products to procurement authorities at low prices, and are typically nonprofit. A nonprofit organizational character might well be the defining characteristic of a PPP or PDP. While most, if not all, originator pharma companies make some portion of their products available at low prices, or donate them at no cost, these activities are not a defining characteristic.

Major archetypes of existing PPPs/PDPs include (but are not limited to) Drugs for Neglected Diseases Initiative (DNDi), Global Health Innovative Technology Fund (GHIT), Medicines for Malaria Venture (MMV), GAVI Alliance, and Foundation for Innovative New Diagnostics (FIND). Each of these organizations includes governmental and nongovernmental funding sources, works in cooperation with private sector companies, and makes its products available on a low-cost/nonprofit basis. A new entry into the PPP environment is the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X. Each of these examples is discussed briefly here.

A *DNDi*

DNDi (or Drugs for Neglected Diseases Initiative) was created in the early 2000s at the initiative of initiative of Médecins Sans Frontières (MSF or Doctors without Borders) to address a pronounced lack in funding for R&D efforts to address so-called neglected

See, e.g., U.S. Dep't of Veterans Affairs, *Doing Business with VA* (2015) (showing Veterans Administration expenditures on drugs, pharmaceuticals, and hematology in fiscal year 2014 (including through related programs), totaling $8.261 billion).

[14] Cents. for Medicare and Medicaid Servs., *National Health Expenditure Data* (2016), available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet.html (last visited June 12, 2018). Dollar ($) amounts mentioned in this chapter refer to U.S. dollars.

[15] As states are major procurers of pharmaceutical products as well, combined federal and state expenditures certainly exceed one half of total pharmaceutical expenditures. *See Pharmaceuticals: Facts, Policies, and NCSL Resources*, National Conference of State Legislatures [NCLS] (Jul. 2, 2017), www.ncsl.org/research/health/pharmaceuticals-facts-policies-and-ncsl-resources.aspx. Total pharmaceutical expenditures exceeded $370 billion. *See* Richard Gauchi, PowerPoint presentation, Prescription Drugs: Overview and Update (Nov. 2, 2015).

diseases.[16] It is by now generally accepted that the predominant exclusivity based model for aggregating investment for R&D on new drugs fails to address diseases affecting patient populations with limited financial resources, because of the absence of sufficient financial demand. At the time DNDi was formed, its approach was pathbreaking.

DNDi relies on contributions from governments and foundations to finance its R&D efforts. It has been among the most successful of PPPs in its fund-raising efforts, and it has been notably successful in developing new therapies, including improved formulations, and recently new chemical entities. DNDi has successfully partnered with originator companies in making use of proprietary compound libraries, as well as in making use of high-throughput screening equipment. DNDi is able to enter into such favorable arrangements because it has not been in competition with the originators for lucrative markets.

DNDi is expanding its mandate to address neglected patients as well as neglected diseases.[17] For example, DNDi has recently entered into agreements under which it is working toward making available a very low cost alternative to the Hepatitis C treatments offered by the major originators; in particular, it has been working with an Egyptian generic company that is using a nonpatented compound similar to sofosbuvir. Although it remains to be seen, the alternative under development by DNDi and its partners would be an effective low-cost Hep-C treatment substitute that can be used in high income countries, assuming (and this is a major question) that governmental authorities (including judges) in the high income countries are willing to accept the nonpatented or noninfringing status of the drugs.

B *GHIT*

GHIT (or Global Health Innovative Technology Fund) is organized in a manner similar to DNDi.[18] Its main funding source is the government of Japan, and its private sector working partners are principally Japan-based originator companies. GHIT funding partners also include major foundations, and it works with UNDP on its access programs.

GHIT has targeted several diseases prevalent among low-income populations in sub-Saharan Africa, and is engaged in clinical trials of several of its drug candidates.[19] GHITs access policy indicates that it will make treatments available to low-income populations on a nonprofit basis.[20] GHIT and DNDi are partnering on certain projects, including

[16] *See* DNDi, www.dndi.org (last visited Jul. 14, 2017). DNDi is an acronym for "Drugs for Neglected Diseases initiative." *E.g.*, DNDi, From Neglected Diseases to Neglected Patients and Populations (2015), www.dndi.org/wp-content/uploads/2016/08/DNDi_AR_2015.pdf.

[17] The reference to patients is an acknowledgment that when new treatments are developed they may not be accessible even for patients in higher income countries. Making available lower-priced versions of existing drug treatments is now part of DNDi's mission.

[18] *See* Global Health Innovative Tech. Fund [GHIT], www.ghitfund.org.

[19] *See, e.g.*, Access and Delivery P'ship [ADP], Issue Brief: An Integrated Approach to the Discovery, Development and Delivery of New Health Technologies for Malaria, Tuberculosis, and Neglected Tropical Diseases: Tanzania (2016), http://adphealth.org/upload/resource/Issue_brief_case_study_of_Tanzania.pdf.

[20] GHIT Access Pol'y, www.ghitfund.org/afag/policies.

GHIT funding of DNDi/pharma projects to identify novel drug targets and to screen for potential treatments for leishmaniasis and Chagas disease.[21]

C *MMV*

MMV (or the Medicines for Malaria Venture) refers to itself as a PDP, although like DNDi and GHIT it is funded through a combination of governmental, foundation, and other philanthropic sources (including private sector companies), with a more specific focus on development of antimalarials.[22] In terms of access, MMV indicates that its objective is to assure that new medicines will be made available at an affordable price, typically with no profit and no loss, through public sector channels. It seeks to retain intellectual property rights to drugs developed through its funding, and a royalty-free license for use in its malaria programs in low resource countries.[23]

D *GAVI*

GAVI Alliance (formerly Global Alliance for Vaccines and Immunizations) is a PPP with the principal mission of providing access to low-cost vaccines to children in developing countries.[24] Principal seed funding for GAVI came from the Bill and Melinda Gates Foundation, and its main partners are the World Health Organization (WHO), UNICEF, and the World Bank. GAVI's business model involves pooling developing country demand for vaccines and establishing advanced market commitments to purchase,[25] thereby providing secure funding for vaccine producers.[26]

E *FIND*

FIND (or the Foundation for Innovative New Diagnostics) was founded to promote the development of diagnostic tests for poverty-related diseases, including tuberculosis, malaria, sleeping sickness, HIV, and Chagas disease. Using funding from foundations, governments, UNITAID, and working in cooperation with private sector companies, WHO TDR, and others, FIND has successfully developed low-cost diagnostics adapted to local conditions.

FIND negotiates preferential pricing arrangements from diagnostic suppliers for the public sector in low and middle income countries, and health providers must commit to

[21] *See, e.g.*, Press Release, DNDi, GHIT Fund Reinforces Its Support to DNDi Leishmaniasis and Chagas Disease Projects (Mar. 30, 2017), www.dndi.org/2017/media-centre/news-views-stories/news/ghit-reinforces-support-to-dndi-for-leish-and-chagas/.

[22] *See* Meds. for Malaria Venture [MMV], www.mmv.org/.

[23] *Socially Responsible Agreements*, MMV, www.mmv.org/partnering/socially-responsible-agreements, (last visited Nov, 5, 2016).

[24] *See* www.gavi.org (last visited Jul.16, 2017).

[25] *See, e.g.*, AMC Secretariat of Gavi, *Advance Market Commitment for Pneumococcal Vaccines Annual Report 1 January–31 December 2015*. Principal suppliers under this advance market commitment regime for pneumococcal vaccines in 2015 were GSK and Pfizer. *See Pneumococcal AMC*, Gavi www.gavi.org/funding/pneumococcal-amc/.

[26] A PPP primarily designed to secure affordable treatments developed by third parties is sometimes referred to as a product access PPP, to be contrasted with the PDPs such as DNDi, GHIT, and MMV.

low-margin markups.[27] With respect to intellectual property, industry partners must assign FIND a royalty-free license to use the technology in public and nonprofit sectors in high endemic countries; the industry partners retain rights for high income countries and in the private sector in developing countries.[28]

F *CARB-X*

A recent entry into the PPP sphere is Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, which is housed at Boston University School of Law, and brings together the US Department of Health and Human Services (HHS), through its Biomedical Advanced Research and Development Authority, or BARDA, division, as well as the NIH NIAID, the UK Wellcome Trust, and the AMR Centre, (a new UK-based funder of biomedical research and accelerator). CARB-X will initially engage two R&D accelerators, Massachusetts Biotechnology Council in Cambridge, Mass., and the California Life Sciences Institute of South San Francisco.[29] CARB-X has commitments for over $40 million in funding for its first year of operation, and up to $350 million over a five-year period.

At this early stage, the licensing and access policies of CARB-X are being worked out.[30] Potential models include Wellcome Trust policies for antibiotics. The leadership of CARB-X also takes note of the Davos Declaration and accompanying Industry Roadmap for Progress on Combating Antimicrobial Resistance signed by thirteen pharma companies and that includes supporting affordable access.[31]

IV Advantages and Limitations of PPPs and PDPs

A *Current Limitations on Scope*

A defining characteristic – if not "the" defining characteristic – of each of the PPPs described earlier is that each was formed, and each operates, to address a situation of market failure. The R&D funding directed to these organizations in most cases comes from government or foundation sources that are addressing problems largely unrelated to domestic public health system needs of industrialized states, with the exception of the newly forming CARB-X. In this regard, the PPPs are addressing public health needs that are largely confined to low- and low-middle-income countries, although it is important to note that DNDi has recently shifted its focus toward neglected populations as well as neglected diseases so as to signal broader concern for low-income populations throughout the world.

[27] *Negotiated Product Pricing*, FIND, www.finddx.org/pricing/.
[28] *Business Model*, FIND, www.finddx.org/business-model/.
[29] *See* www.carb-x.org/ (last visited Jul. 16, 2017).
[30] Email from Kevin Outterson, Executive Director, CARB-X, to author (Oct. 31, 2016) (on file with author).
[31] *See* Rev. on Antimicrobial Resistance [AMR], Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance (Jan. 2016), https://amr-review.org/sites/default/files/Industry_Declaration_on_Combating_Antimicrobial_Resistance_UPDATED%20SIGNATORIES_MAY_2016.pdf (last visited Jul. 16, 2017); *see also*, Int'l Fed'n of Pharm. Mfrs. & Ass'n [IFPMA], Industry Roadmap for Progress on Combating Antimicrobial Resistance – September 2016, www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf (last visited Jul 16, 2017).

None of the aforementioned PPPs assert as its mission a transformation of the global model for developing new drugs across the range of diseases, or for promoting access to them. And none of them involve self-sustaining revenue generation models.

B *Extending the Scope of PPPs as Alternative R&D Models*

With that said, however, DNDi may help to illustrate that it is possible to build a new drug development model that eliminates the for-profit intermediary financier from the process. In other words, DNDi serves as the nonprofit intermediary hub, performing the function that a major originator company typically performs, that is: (1) identifying disease targets; (2) engaging third parties to perform identification of promising compound candidates; (3) selecting candidates for clinical trials; and (4) managing the process of registration, and introduction of the product onto the market. DNDi has indicated that its costs of developing new drugs are substantially lower than those that are publicly suggested by the major originator companies (in the order of $150 million as compared with well over $1.5 billion).[32]

Nonetheless, DNDi has to date addressed only a small portion of the potential set of disease candidates that challenge global public health, and it has had the advantage of access to compound libraries already created by originator companies. At an expanded scale, could the DNDi type of "hub" operation work with the much larger capital requirements and expenditures, such as those involved in the development of new biologic drugs, and where the risks of failure are large? Is a nonprofit entity capable of administering large-scale funding in a manner that does not entail inefficiency and waste, or corruption?

These are not insignificant or merely speculative issues. While the profit motive may induce certain types of bad behavior, other motivations for bad behavior with respect to government/public and/or nonprofit administration may be equally problematic. The private sector is brutal at punishing unsuccessful actors. It may be more difficult to discipline entrenched nonprofit or public authorities.

C *Discipline and Incentive in R&D Models*

Introducing some type of performance-disciplining measures into a nonprofit hub model could guard against inefficiency, waste, and corruption, or more prosaically against poor decision-making. The management team of a PPP would need to be assessed against some criteria, and the system would need to be highly transparent. In some respects, PPP management would be in a position not entirely dissimilar from the officers of for-profit originator companies, but without the very high salaries and stock-option allocations. A major difference, however, would be that the performance indicator would not be profit; instead, it would be success in regard to addressing public health requirements.[33]

[32] For details regarding wide variations in estimates of funds needed to develop new drugs, *see* Abbott, *supra* note 3.

[33] The directors and officers of for-profit corporations have fiduciary duties to the corporation and its shareholders, and the directors and officers of nonprofit organizations have fiduciary duties to the organization. The text reference to the profit motive for the typical for-profit pharmaceutical enterprise is not directed to the legal standard under which organizational responsibility may be determined, but rather the internal and external assessment by which the success of a corporation and its ability to attract investment is evaluated by the financial community.

One could argue that the existing originator model assesses corporate officers and directors in relation to success in addressing public health requirements, with profit serving as a proxy. If a company does not develop successful new drugs, it does not profit. Therefore, the standard Wall Street model does what the nonprofit hub model would seek to do. The problem with this analogy is that things done in the pursuit of profit are not the same things that should be done in the pursuit of public health. For example, a public health approach would not encourage dispensing of drugs like antipsychotics or attention deficit disorder controllers to senior citizens or young patients for the sake of increasing sales. This type of excessive marketing and promotion is a common occurrence within the for-profit pharmaceutical sector, for which companies are only from time to time penalized.

What type of incentive/discipline structure would be appropriate to a PPP hub? The following guidelines are proposed as a starting point:

1. Salaries for senior officers/staff would need to be commensurate with high-paying university positions that are generally sufficient to attract talented scientists and managers.
2. Management would be required to lay out a business plan with defined targets, and such plan would be reviewed by an appropriate supervisory board, and perhaps a team of external expert reviewers. Management performance would then be assessed against success in achieving the goals laid out in the business plan. To the extent feasible, the plan would include objective indicators in the interest of reducing subjective judgment and bias on the part of all concerned.[34]
3. Financial dealings would be transparent and audited. Because the objective of the enterprise would be the advancement of science, the default position with respect to information concerning R&D would be transparency. This means that competing PPPs might make use of published information, which could theoretically lead to multiple efforts directed toward the same disease target. This risk, however, should be one that is shared among the various PPP hubs. If the possibility for patenting and market exclusivity claims on PPP innovation by originator for-profit entities exists, this might cause a reassessment of transparency policies, and might require defensive patenting of discoveries.

D *The Riddle of Capital Aggregation*

1 Financial Nature of Distinguishing Characteristics

At the outset of this chapter, it was noted that all or virtually all new drug R&D involves a combination of public and private funding. It has long been the case that major originator pharma companies essentially act as clearinghouses for third-party research, providing the function of analyzing and assessing external work, and making decisions regarding where to invest in clinical trials and subsequent approval processes. When you combine government R&D funding (as in the case of the US NIH) with the R&D clearinghouse function of the major originator company, the main distinctions between

[34] For example, the DNDi Business Plan 2015–2023 sets out a number of objective targets in terms of treatments and new chemical entities to be developed, and these objectives could be used as indicators against which the performance of the management team could be assessed. DNDi, DNDi Business Plan 2015–2023 (2015), www.dndi.org/wp-content/uploads/2009/03/DNDi_Business_Plan_2015-2023.pdf.

the for-profit R&D enterprise with the archetypal PPP like DNDi are financial in nature, specifically: (1) the source of external capital, which is raised through public securities markets (like the New York Stock Exchange); and (2) the for-profit firm's revenues, which are generated on behalf of private securities holders rather than some public fund.

To make matters a bit more confusing, as stated earlier, a large proportion of stock in the United States is owned by pension funds and retirement accounts, so that effectively the profits are returned to a fairly broad segment of the public.[35] In this regard, the originator pharma companies based in the United States (and analogously in Europe) could be viewed as the custodian of the assets of individuals living within the United States, who are investing those assets toward R&D. Other than the officers of the originator companies who may be taking a larger share of the revenues than appears socially responsible, one can argue that high pharmaceutical prices reflect that proportion of US individuals owning stock paying themselves. Those outside the United States who are adversely affected by high prices are those who do not own such assets.

E *Money in the System*

There are a substantial number of variations on proposals for aggregating R&D capital outside the current predominant model based on patents and regulatory exclusivity. Any alternative to the current model will require some means to aggregate capital, make determinations regarding where to invest that capital from the R&D standpoint, select among promising drug candidates regarding whether to move forward (including whether to initiate clinical trials), and initiating and supervising the registration and approval process before the relevant national drug authority. All of these today are functions that are largely performed by private sector originator pharma companies.

Probably the most compelling argument supporting alternative mechanisms for aggregating capital is the enormous amount of money in the current global pharmaceutical system that manifests annual sales revenues substantially greater than $1 trillion.[36] Using generous estimates, only about $150 billion of that revenue finds its way into private and public R&D efforts.[37] Of course there are costs attributable to producers and distributors of drugs over and above the R&D component, but even a generous accounting for costs probably gets to about $500 billion. The other 50 percent of sales revenue goes somewhere else. The challenge is to find a way to channel procurement demand into R&D

[35] According to Goldman Sachs: "Households directly own 38 percent of the US equity market," … "However, the total effective household ownership is closer to 80 percent when combined with indirect ownership in the form of mutual funds (20 percent), pension funds (16 percent), and insurance policy holdings (7 percent)." Sam Ro, *CHART OF THE DAY: Here's Who Owns the Stock Market*, Bus. Insider, March 13, 2013, www.businessinsider.com/chart-stock-market-ownership-2013-3 (last visited June 12, 2018).

[36] *See, e.g.*, IMS Inst., *The Global Use of Medicines: Outlook through 2016* (2016), www.imshealth.com/files/web/IMSH%20Institute/Reports/The%20Global%20Use%20of%20Medicines%20Outlook%20Through%202016/Medicines_Outlook_Through_2016_Report.pdf (last visited Jul. 16, 2017).

[37] US PhRMA estimates that its members spent $51.2 billion on R&D in 2014. Pharm. Res. and Mfrs. Of Am. [PhRMA], *2015 Profile Biopharmaceutical Research Industry* (2015), www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf. Added to that would be approximately $30 billion in research funding from the US NIH. Rest of world pharmaceutical R&D is typically less than US private sector spending. *See* Org. for Econ. Cooperation and Dev.[OECD], *Research and Development in the Pharmaceutical Sector* (2015), www.oecd-ilibrary.org/docserver/download/8115071ec070.pdf?expires=1478360602&id=id&accname=guest&checksum=9DC067062F87B1CE6B0D0F72453F580F. Given that the industry figures are largely self-reported, $150 billion should be considered a generous estimate.

pools that are well managed and could substitute for originator companies that appear to charge a very large premium for their services.

F *Delinkage as a Key Concept*

Delinkage involves separating the R&D function from the production, sale, and distribution functions.[38] Under this model, the production, sale, and distribution of pharmaceuticals would be treated as competitive business unencumbered by market exclusivity. Delinkage is the situation largely present in the existing generic pharmaceutical industry. Generic pharma producers still must comply with a host of regulatory requirements, including compliance with GMP, registration, and so forth. Delinkage, therefore, does not presume unregulated pharmaceuticals markets.

Delinkage is designed mainly to protect the procurement authority and consumer from high pharmaceutical prices. The predominant model for R&D relies on patents and market exclusivity to generate high rates of return for originator companies that use some portion of profits to invest and reinvest in new drug development and other improvements.[39] The essential objective of delinkage is to isolate R&D costs, and pay for them *other than* through sales and distribution revenues. It does not necessarily follow that R&D costs will decline. It is generally assumed, however, that by removing the distortions in the current system stemming from the need to generate large profits, there will be systemic savings. It remains that capital for investment in R&D must come from somewhere, if it is not coming from high-margin pharmaceutical sales.

G *Government Taxing and Spending as a Source of Funding*

The government secures its financial resources from the collection of taxes, and taxes come from the same individuals and businesses that purchase pharmaceutical products. So, the government could establish a fund for pharmaceutical R&D, which is allocated to PPP hubs that are responsible for developing new drugs, taking them through the clinical trial phase, and making them available to generic producers. With regard to production, there may need to be limits on pricing even without market exclusivity if it appears that excessive prices are charged. In this model, margins should be low.

Using the United States as an illustration, the NIH already allocates a very large pool of R&D funds to pharmaceutical research, and has established methodologies for selecting R&D projects. It is not a stretch to suggest that these R&D projects move forward some

[38] *See, e.g.*, Michelle Childs, Director Policy Advocacy, Medicines Sans Frontieres [MSF], *The de-linkage of the cost of research and development and the price of health products*, Powerpoint presented at meeting of WHO Committee of Experts Working Group: Financing and Coordination (Nov. 16–19, 2011).

[39] As noted earlier, the system has its flaws, not the least of which is that much of the profit is used for purposes other than investment in R&D and production, including sometimes excessive executive salaries, buybacks of stock unsupported by sound business justification, and other means of allocating revenues that do not serve public health purposes. The poster child for excessive pharmaceutical salaries is the former CEO of Pfizer, Hank McKinnel, who walked away with approximately $180 million in compensation after leading the company through a string of R&D failures. *See* The Associated Press, *Pfizer's Ex-Chief to Get Full Retirement Package*, N.Y. Times, Dec. 22, 2006, at C2. Flaws include reliance on generation of high-margin sales to sustain the model. Sales promotion may perversely encourage overprescribing. *See* Abbott & Dukes, *supra* note 10, at 163–92.

additional steps, such as into the development of production process technologies, involved in the translation of basic discoveries into commercially marketable new drugs. Those additional steps could be undertaken through the PPP hub entities that would essentially be subcontractors to NIH.

Potential drawbacks are also foreseeable. While governments can be staffed with teams of experts, peer review, and so on, there remains the question whether bureaucracies are good at allocating capital. It is not clear that government bureaucracies are better institutions to pursue these tasks than private industry. Nonetheless, a system that relies on an NIH-type institution to identify targets of R&D and allocate government resources is an alternative to the existing model.

A model that moves from private sector funding through aggregation of risk capital to a public sector funding model that relies on funds from the government budget (taken from taxation) would presumably entail impact on the general economy of a country. Conceptually, employment might remain more or less stable, but whether inflows into the taxation pool would remain sufficient is a question. If indeed originator pharma companies pay fairly low taxes, this may undercut an argument in favor of maintaining the existing private sector model.[40] While employees of pharma companies presumably pay income taxes, these employees would similarly pay taxes if funded by the government budget.

Consider, for example, that a substantial part of the US government healthcare budget (state and federal) is devoted to the purchase of originator pharmaceuticals. If procurement outlays were cut substantially, federal and state tax requirements would correspondingly be lower. This shift in expenditure should not adversely affect existing nonprofit R&D entities that would continue to be relied upon for innovative endeavors even if their operating models might be more mainstream in a delinkage environment.

H *Insurance Pools*

An alternative to government funding is privately managed insurance pools.[41] Health insurers already aggregate the funding to address the demand for pharmaceutical products their patients require. Health insurers would have a vested interest in reducing incidence of disease since this would result in reduced outlays. Since the insurance companies already aggregate funds, conceptually these funds could be allocated to *ex ante* R&D as well as to *ex post* procurement. If R&D costs could be substantially reduced through some type of low-margin R&D hub facility, *ex post* expenditures could be substantially reduced. No doubt, this complex concept needs to be worked out in its details. Nonetheless, as private health insurers are the second largest funder of pharmaceutical procurement behind the federal and state governments, the pools of funds

[40] It appears, for example that Pfizer has paid almost no income taxes within the United States over the past several years, leaving most of its profits offshore. *10 Corporate Tax Dodgers You Should Know About*, Moyers & Company (May 29, 2014), http://billmoyers.com/2014/05/29/10-companies-that-dodge-corporate-taxes/; Chad Stone, *Reality Check on Corporate Income Tax Rates*, U.S. News, Nov. 13, 2015, www.usnews.com/opinion/economic-intelligence/2015/11/13/reality-check-on-corporate-income-tax-rates.

[41] For a proposal involving intergovernmental risk pools, see Jeffrey Mark Erfe, *Reducing Outbreaks: Using International Governmental Risk Pools to Fund Research and Development of Infectious Disease Medicines and Vaccines*, 87 Yale J. Biol. Med. 473, 473–479, (2014) www.ncbi.nlm.nih.gov/pmc/articles/PMC4257034/.

aggregated by these insurers are a logical possibility for repurposing. One foreseeable difficulty with such an idea is that insurers might elect to free-ride on each other's investments, so a mechanism would need to be organized to spread outlays through a major collective pool.

I *The WHO Consultative Expert Working Group (CEWG) R&D Treaty Proposal*

It should be evident that the idea of the PPP hub as implementing mechanism for R&D may be the type of arrangement contemplated by proposals at the WHO for an R&D Treaty.[42] The general aim of the R&D Treaty is to combine an interest in new models for R&D with some type of mechanism that ensures a base level of governmental funding, while at the same time guarding against the potential free-rider problem. More specifically, would taxpayers in the United States be willing to engage in nonprofit tax-payer based funding of R&D projects if the resulting new drugs were made freely available to a global population, including other countries and regions that are capable of investing their own resources in R&D?

J *Are Free Riders a Real Problem?*

It is not clear that the free-rider problem is the impediment it might be made out to be. The current global framework for biomedical R&D relies very substantially on investments undertaken in the United States, and to a somewhat lesser extent Europe and Japan. The balance of investment and purchasing power may be shifting, with China playing a growing role, and India presumably not far behind. Would these countries give up their scientific pursuits of new drugs because drugs might be available based on the efforts of US researchers? If there was a serious free-rider problem, could the United States take some type of trade-balancing action, such as the collection of R&D offset tariffs, to address the problem? Such an action might break the existing WTO mold, but the WTO mold is there to be broken as the circumstances may justify. It seems unlikely that the advanced negotiation of an R&D Treaty is a necessary prerequisite to a move toward different models in the United States.

K *Treatment of Disease and Lifestyle Drugs*

Although the system described earlier might result in substantially lower pharmaceutical prices for new discoveries of drugs to treat important diseases, this would nonetheless leave the market for nonessential drugs like beauty-enhancers, sometimes referred to as lifestyle drugs. The market for cosmetic medicines and other lifestyle drugs is a very large one, and it should not be dismissed as some kind of dysfunctional anomaly. Could a parallel system that addresses the development of new types of Botox work alongside an expanded PPP hub model?

[42] *See*, for description of proposals, Ryan Abbott, Opinion, *Inside Views: Potential Elements Of The WHO Global R&D Treaty: Tailoring Solutions For Disparate Contexts*, Intellectual Property Watch (Jan. 29, 2013), www.ip-watch.org/2013/01/29/potential-elements-of-the-who-global-rd-treaty-tailoring-solutions-for-disparate-contexts/

It is foreseeable that new drug development could move along different tracks depending upon the subject matter field of R&D. It is, however, important to note that the cost savings that might be generated by moving toward a PPP hub model for therapies to treat disease could be affected by a parallel system addressing lifestyle concerns if both systems were integrated in some type of pooled insurance arrangement. If lifestyle drugs are made available through a combined pool, and prices and demand are high, the result could be a similar one for end users of disease therapies if their insurance costs reflect pool demand.

V Conclusions: Innovation and Access

Forms of capital aggregation, institutional structure, and decision-making are fluid. A good argument can be made on behalf of each public and private sector R&D, or some combination of the two. At the end of the day, the fundamental question from the R&D side is whether progress will be made in preventing and treating disease, and at what cost. From the human rights and social impacts side, the question is whether the preventatives and treatments will be made available to those who need them. Ultimately, whether treatments will be made available depends upon the access policy. Unless we know what the access situation is going to be, which could be referred to as the downstream impact, it is difficult to make decisions regarding the optimal upstream model. If funds are not going to be available to purchase and distribute treatments, it is not particularly helpful to develop them. And, without knowing whether those funds will be available, it is difficult to make decisions regarding the amount of capital that should be aggregated and invested. The systemic issues are essentially circular.

By defining the patient access situation in advance, the public or private investor can better determine whether investment should be undertaken. There should be a largely predictable outcome in terms of sales and/or procurement costs. The distortion in the current system or model is that private investors can exploit vulnerable patient populations once treatments are developed. Though private investors assert that price controls are anathema because they limit the profitability of investment, and therefore the amount of risk that investors are willing to take, determining the size of the market and setting the price in advance would allow private investors to scale their investments to realistic market outcomes. If there is a lack of investment based on inadequate potential market, public funding in the form of subsidies or advance market commitment can step in to supplement with additional funding.[43]

Delinkage is likely to play a significant role in alternative models used for funding new drug R&D. It envisages generic competition in the downstream market for pharmaceuticals with concomitant low prices. Price regulation can possibly serve a function similar to that of delinkage. In other words, forms of market exclusivity can be used so long as

[43] It is an interesting to consider whether a governmental authority, such as the US Department of Health and Human Services, or the Centers for Disease Control, could calculate potential disease market baskets and maximum procurement costs, and limit medicines providers to that aggregate basket, including a set per treatment price. Advance commitments could be established with bids from the private sector, factoring in R&D costs. If sufficient interest is not shown in the bidding, government could step in to supplement the price.

there is an alternative mechanism for assuring that prices are affordable enough to promote optimal accessibility.

There are many potential alternatives to the predominant model under which new drugs are developed primarily by using patents and marketing exclusivity as means to aggregate capital through the promise of high prices. Leaders of the originator pharmaceutical industry not uncommonly express the idea that if the system is not broken, why fix it?[44] They point to the risk that attempts to modify the existing system will result in a shortfall of funds invested in R&D.

However, a mix of public and private funding of new drug R&D is an existing reality. The real issue is whether shifting control to models that reduce profit motivation and include more publicly oriented management would lead to better outcomes. Experimentation is warranted. Existing PPPs and PDPs are demonstrating that alternative models are workable in some contexts. The main question is whether and how their success can be scaled.

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