EVANS SCHOOL OF PUBLIC POLICY & GOVERNANCE

UNIVERSITY of WASHINGTON

Evans School Policy Analysis and Research (EPAR)

Review of Literature on Factors Affecting Private Sector Investment in Global Health R&D

EPAR Technical Report #345: Executive Summary

Professor C. Leigh Anderson, Principal Investigator
Professor Travis Reynolds, co-Principal Investigator

Pierre Biscaye, Karen Chen, David Coomes, Elan Ebeling, Vivian Gor, Trygve Madsen, Emily Morton

C. Leigh Anderson, Carol Levin, & Travis Reynolds

December 5, 2017

Executive Summary

The share of private sector funding, relative to public sector funding, for drug, vaccine, and diagnostic research & development (R&D) differs considerably across diseases. Private sector investment in overall health R&D exceeds $150 billion annually, but is largely concentrated on non-communicable chronic diseases (Jamison et al., 2013) with only an estimated $5.9 billion focused on diseases that primarily affect low and middle-income countries (LMICs) (West et al., 2017b).[1]

It would be easy to conclude that private sector investment choices simply reflect the most profitable use of funds or the most comfortable risk-return tradeoffs, especially considering the high opportunity cost of capital earning large returns in high-income country (HIC) markets. There are, however, examples of privately funded R&D, blended financing, and public-private partnerships targeting diseases in LMICs. The detailed story, therefore, is likely more complex, with possibilities at the margin for catalyzing more private sector investment by increasing returns, lowering risk, or overcoming institutional disincentives for private R&D funding.

We look more closely at these nuances by examining the evidence for five specific disincentives to private sector investment: scientific uncertainty, unstable policy environments, limited revenues and market uncertainty,

Price, information & market power: influences on private sector global health R&D investment

- Low or uncertain LMIC product prices relative to prices in the U.S. or other HICs limit private global health R&D investment

- LMIC market data gaps further hinder revenue forecasting and reduce firm or product market entry

- Though revenues from global health R&D may be low or uncertain, costs are often high, sunk and incurred upfront with certainty

- Relatively strong downstream market power may make it cheaper to purchase (license) rather than produce internally (conduct R&D)

- Proprietary science and LMIC health science data gaps represent further barriers to private global health R&D (e.g., data science, bioengineering)

---

[1] In this paper, we use the term global health R&D to refer to R&D that targets diseases primarily affecting low- and middle-income countries (LMICs) while overall health refers to R&D that targets any disease, both in LMICs and in high-income countries.

high fixed and sunk costs, and downstream rents from imperfect markets. Though all five may affect estimates of net returns from an investment decision, they are worth examining separately as each calls for a different intervention or remediation to change behavior.

Our goal of examining these separate components of private sector investment decisions in global health R&D is made challenging by the scarcity and unevenness of publicly available information. Our strategy, therefore, both for painting as full a picture as possible and having confidence in our findings, is to reference - and check against – multiple sources. An earlier report (West et al., 2017b) draws on consultations with over two dozen experts on global health R&D from multiple sectors and case studies of leading examples of venture capital investments and innovative finance. In this report we conduct an expansive review of the grey and published literature that allows us to analyze overlaps and differences in the investment challenges highlighted by expert consultations and by academic and industry research.[2]

Our review draws on literature from five primary academic search databases, five supplemental search databases, ten private pharmaceutical company websites, and twelve philanthropic and public organizations involved in health R&D worldwide. The literature reviewed focuses primarily on global health R&D, but in order to capture factors possibly influencing private sector "non-investors" we did not limit results to health R&D specific to LMICs. The searches yielded 285 sources that discuss private investment in 47 individual diseases that we use to extract information on company characteristics, research and development characteristics, and potential market returns. All sources were published in the past 15 years, relate to private sector R&D investments targeting either drugs, vaccines, or diagnostics, and include findings on R&D at any point from pre-clinical research through Phase III clinical trials.[3]

We coded the resulting sample of literature using a framework derived from public goods theory and theories of private firm behavior, which includes five disincentives hypothesized to inhibit private sector investment in global health R&D, though not all equally unique to R&D for LMICs: *Scientific uncertainty*; *Uncertain, unstable, or weak policy environments*; *Limited revenues and market uncertainty*; *High fixed and sunk costs*; and *Downstream rents from imperfect markets*.   Some of these factors are more frequently cited than others, as summarized below:

- *Scientific uncertainty (seldom mentioned)*: Uncertainty surrounding the results of scientific research is rarely discussed as a primary factor deterring private investment in global health R&D, although some sources provide estimates for the probability of success for medical product research when describing private sector investment decisions. Only four studies emphasize the complexity of research, access to existing research and the limited volume of existing knowledge as specific factors influencing private R&D investment decisions.

- *Uncertain, unstable, or weak policy environments (frequently mentioned)*: Geo-political risks and

---

[2] An upcoming report relies on publicly disclosed industry-reported financial data.

[3] Stages of clinical trials as defined by the WHO: "Phase I: Clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects). Phase II: Clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety. III: Studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely. IV: Studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use" (*WHO: http://www.who.int/ictrp/glossary/en/#TrialPhase*).

unstable macroeconomic and policy environments are widely cited in industry reports as deterrents to private sector investment in global health R&D, but most sources offer little specificity. Uncertainty in returns stemming from the regulatory environment, regulatory costs, and weak or uncertain intellectual property (IP) protections are among the more commonly cited policy challenges for private health R&D, rather than more general macroeconomic volatility.

- *Limited revenues and market uncertainty (frequently mentioned)*: Considerable evidence points to limited market potential (i.e., low expected revenues) to explain underinvestment in diseases affecting LMICs. However only two sources cite small market size as a deterrent to private investment – most others highlight pricing (low and/or uncertain LMIC prices) as the major deterrent to private R&D. The interaction between competition and expected revenue streams also appears in the literature: eight sources report on how low (high) prices are deterring (incenting) private R&D investment, depending on the treatment. Four additional sources look at prices and willingness-to-pay across high- and low-income countries, suggesting that companies assume different prices for the same drug when estimating potential future revenues across different markets. Incentives to invest in R&D targeting diseases prevalent in the U.S. and other high-income countries are higher given the ability to set prices at what the market will bear, relative to prices in LMICs which may be lower, regulated, or unknown.

- *High fixed and sunk costs (often mentioned)*: Multiple studies mention costs though only five specify the high fixed and/or sunk costs of global health R&D in private investment decisions. Clinical trial costs, specialized equipment, subject area expertise, and payments for access to previous research via royalties or other IP payments, are "sunk" to the extent that these investments are difficult to repurpose. The reviewed literature presents a range of cost estimates for bringing a drug to market between $802 million and $2.2 billion. However, critiques of the most widely cited cost-estimate studies emphasize the "constructed nature of R&D cost estimates" (Light & Warburton, 2011, p. 47) and the degree to which cost estimates may be inaccurate, and depend heavily on assumptions and available data.

- *Downstream rents from imperfect markets (often mentioned)*: Theory predicts that the nature of the health R&D industry creates incentives for large firms with downstream capacity to increasingly move resources out of R&D, if they are able to purchase rights to the results of upstream R&D at lower cost than producing those R&D outputs themselves. Upstream competition can make it more profitable for large firms with a downstream presence to purchase patent rights rather than invest in their own R&D, which Roy & King (2016) note is a common industry practice. Five sources describe private R&D efforts to improve the efficacy or effectiveness of existing treatments — so-called "me-too" drugs — as examples of private investors' preference to secure downstream rents rather than invest in new health R&D ventures. In other cases policy incentives may favor downstream private investment, or public and philanthropic funding may be subsidizing or crowding out upstream research in ways that discourage private funding. Three sources suggest limited patent windows may encourage private firms to divert their resources towards marketing rather than additional R&D, in order to maximize profits during the period of exclusivity (Love, 2005).

We find some corroboration between expert opinions as reported in West et al. (2017b) and the current review of literature. West et al. (2017b) offer six main explanations for limited global health private sector R&D: *Limited Markets for Certain Diseases* (illnesses that affect small numbers), the *Cost of Drug Development* (long development cycle), *Geo-political Risks* (risks to long-term investments and revenue streams), *Macroeconomic Difficulties* (recession, exchange rate, and interest rate risks), *Poor Health Governance* (difficulty in products reaching intended beneficiaries), and a *Lack of Systematic Data* (evidence on what works). In our review of literature there is common mention of the challenge of limited markets, though the literature reviewed is clear

that in the revenue calculation, LMIC pricing is the primary disincentive (even in cases where the LMIC market size is large), especially relative to drug pricing in the U.S. and other HICs. We also find a common lament in the literature that limited information is available about LMIC markets, making revenue (and in some cases cost) forecasts difficult. Other factors cited by experts in West et al. (2017b) including *Geo-political Risks*, *Macroeconomic Difficulties*, *Poor Health Governance*, and a *Lack of Systematic Data,* are less frequently cited in the literature we reviewed as the key determinants of private sector investment decisions – although all broadly relate to private firms' perceptions of risks and potential revenues associated with R&D investments.

Largely absent from factors highlighted in expert consultations but frequently mentioned in the literature is the effect of an imperfectly competitive market structure that creates economic incentives downstream relative to upstream R&D. This structure potentially grants larger pharmaceutical firms enough market power to buy or license R&D below a competitive market price (rather than conduct their own R&D) and enough market and regulatory authority to sell final products above a competitive market price. We find evidence that the current health R&D market structure is characterized – and likely constrained - by specialization, high entry costs, regulatory rents and privately held information; a result of both the nature of disease research and the policy environment. In a perfectly competitive market, in a situation where the vast majority of private investment is flowing into HIC health R&D, at some point the marginal return to a dollar invested in global health R&D would exceed the marginal returns to further HIC health R&D investment (so long as global health R&D was at all profitable). But in an imperfectly competitive market this threshold may not be realized.

The attractiveness of licensing upstream research rather than conducting R&D internally is likely to increase as more computing and data analysis occur in biotech companies relative to the physical science labs of traditional pharmaceutical companies. Customer and market data collected remotely, via social media, through internet searches, or through other means (utility payments, bank transactions, etc.) contain information that has commercial value by informing market opportunities. And as the industry evolves further from a "chemical compound configuration" to a "biotech/biopharmaceutical configuration" resting on "sophisticated informatics and big data infrastructure," (R&D Magazine, 2016), the potential to easily share market, customer, and health knowledge expands, but so does the opportunity to monopolize it, depending on the policies and other incentives facing private investors.

To the extent that health science and market data are more limited for global health R&D, there is reason to speculate that as the industry evolves an even smaller share of investment will be directed at diseases prevalent in LMICs. Both industry experts and the literature lament the limited market data available to better assess potential market outcomes – yet despite potential industry-wide gains, there is no clear incentive for any individual firm within this sector to either fund or contribute to such a data service.

Though a variety of policy tools exist to promote private sector investment in R&D, including push mechanisms (public research funding, R&D tax credits) and pull mechanisms (advance purchase commitments, orphan drug programs, priority review vouchers, and wild-card patent extensions), evidence of effectiveness is mixed. While we find 42 sources suggesting that some combination of policy tools had a positive impact on catalyzing private R&D funding for diseases more prevalent in LMICs, 11 sources report mixed results, and 3 sources report negative impacts of policies.