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Solutions and Challenges to Curing Global Health Inequality

Innovations Case Discussion:
The Institute for OneWorld Health

The pharmaceutical and biological industries have experienced remarkable growth over the past half century. Today, U.S.-based private firms spend over $40 billion a year on R&D, 10 times the inflation-adjusted levels in 1970.[1] These investments have produced an unprecedented flow of drugs and biologics that save lives and improve the quality of life for millions of people. But this growth in investments and R&D output masks one industry constant: the unwavering propensity of for-profit pharmaceutical firms to neglect the tropical diseases of the developing world. Between 1975 and 1997, over 1,200 drugs were licensed worldwide, but only 13 were developed to treat a topical disease, and only four were developed by private pharmaceutical firms to treat a human form of a tropical disease.[2] The lack of investment in infectious disease drugs stands in stark contrast to the disproportionate burden that infectious and parasitic diseases place on the health of people around the world.

Infectious and parasitic diseases primarily affect people in impoverished nations, where they account for one-third of the total disease burden. In wealthy nations they account for less than three percent.[3] It is therefore unfortunate for individuals afflicted by a tropical disease that pharmaceutical innovation is exclusively a for-profit enterprise. For-profit firms operate under a business model in which R&D investments follow consumers' willingness to pay, not their willingness to live. Thus firms have little incentive to incur the costs of developing a tropical disease drug whose private returns are sure to be low. On occasion, early in the drug development process, firms may even stumble upon drugs with the potential to treat a tropical disease. But if they see no profitable application, they abandon its development. Investors—even those who are otherwise altruistic citizens out-

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side the shareholder meeting—have shown a predictable tendency to steer their managers towards the most profitable projects, even if that means abandoning a drug that has the potential to benefit hundreds of thousands of sick individuals.

In this setting, the Institute for One World Health brings to the market a novel model of drug development. iOWH is a non-profit pharmaceutical company. Free of pressure from shareholders to generate profits, it is committed to improving global health by developing drugs to treat the tropical diseases of poor nations. iOWH's non-profit model allows its managers to maximize a profit function which uses expected clinical benefit or social welfare in place of expected revenue. Thus iOWH has the freedom to undertake projects with substantial social benefit, but limited material benefit.

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But that freedom does not afford iOWH the *ability* to conduct this work. Just like its for-profit counterparts, iOWH faces difficulties raising capital to finance unprofitable R&D. Indeed, just as few private investors are willing to take on certain losses, few people are willing to invest in iOWH projects because the material opportunity costs are so high. Below, I examine the economic challenges inherent in any effort to develop tropical disease drugs, and show how iOWH's business model helps it to negotiate these financing challenges.

BUSINESS MODEL: ADOPTING ORPHAN DRUGS

A key feature of iOWH's business model is its focus on the mid-stream stages of product development. Drug development can generally be partitioned into five phases, each distinguished by its cost and risk profiles. The development process begins as a firm identifies and screens compounds or biologics for desired properties; the firm then optimizes these compounds for use in clinical trials, tests for safety in initial animal and early human clinical trials, tests for efficacy in late-stage clinical trials to apply for drug approval in the local market, and finally manufactures and distributes the drug or vaccine. Relying almost exclusively on scarce donor capital from private foundations, iOWH must use its resources efficiently to maximize the likelihood that it will produce successful drugs.

iOWH specializes in the phases of drug optimization and clinical trials, devoting its efforts to bringing previously developed drugs through clinical trials and the approval process to the point of manufacturing and distribution. To this end, iOWH works closely with pharmaceutical firms to identify drugs that have the potential to treat a tropical disease. In some cases, a firm will realize early in the development process that, despite that potential, such a drug has little commercial

value. These drugs are then abandoned (or "orphaned") despite their promise. In other cases, a firm will discover that a drug has the potential to treat several diseases, including a tropical disease, but it will pursue clinical trials for only the profitable indications.

This is where iOWH enters the development process: it picks up clinical trials testing for tropical disease indications at the point where firms find it unprofitable to continue. On the one hand, this model of development tightly restricts iOWH to a limited set of previously developed drugs whose promise for tropical diseases is often discovered only incidentally. On the other, this model allows iOWH to free-ride on early R&D effort conducted by firms, thereby allowing iOWH to avoid the costs, delays, and exceptional uncertainty associated with creating and screening drugs early in the development process. Viewed from a welfare perspective, iOWH gives society a remarkable opportunity to benefit from what otherwise would have been unrealized social returns on early-stage private R&D expenditures.

Similarly, iOWH's focus on mid-stream development defers to for-profit firms the back-end development processes: the manufacturing and distribution of approved drugs and vaccines. These final steps involve little financial risk and relatively low marginal cost. However, *average* costs to manufacture drugs are enormous, given the substantial investments in human and physical capital required to build manufacturing infrastructure. It is therefore natural for iOWH to outsource these efforts through partnerships with private firms that already have manufacturing facilities and local distribution networks.

Success of iOWH's business model relies on its ability to foster strong relationships with private firms. Collaborating with iOWH does involve some risk for firms. Identifying potential leads requires firms to open their shelves to iOWH; and releasing an orphan drug to the care of iOWH entails surrendering intellectual property. While orphan drugs may have no known profitable application at the time, a profitable application of the drug (or of a derivative) may be discovered at a later date. Therefore, by keeping their orphan drugs in-house, firms retain their option value. When firms consider collaborating with iOWH, they must balance their loss of option value with the potential gains from the collaboration. Similarly, if iOWH's mid-stream orphan drug model is to remain viable, iOWH must develop partnerships with drug manufacturers that are willing to produce at or near marginal cost. Otherwise, a drug whose very development and approval occurred against all odds would become unaffordable.

The partnerships that underpin iOWH's business model must offer tangible benefits to the collaborating firms to offset the intellectual property risks and losses on manufacturing cost margins. One obvious benefit to firms is the positive public relations that may flow from being involved in an iOWH success. Firms may also benefit from greater employee morale and job satisfaction. Bench scientists and clinicians at private firms may value the chance to participate in developing a life-saving tropical disease drug. To the extent that improved morale benefits the firm, executives have an incentive to foster opportunities for their scientists to con-

tribute to iOWH's endeavors. Early collaborations with iOWH are likely to have been supported by a few enthusiastic executives. For collaborations to make the transition from being one executive's altruistic pet project into a more permanent ethos of collaboration depends crucially on early and prominent evidence of iOWH successes. Proof of viability is likely to be as important for fostering private partnerships as it is for generating grant funding. Ultimately, supportive executives at either pharmaceutical firms or grant foundations desire to save more lives, not just to conduct more R&D. iOWH recently succeeded in developing paromomycin to treat Visceral Leishmaniasis, a parasitic disease that prevents the body from producing blood cells; this success has no doubt contributed immeasurably to its long-term sustainability.

CAN WE DEPEND ON THE PRIVATE SECTOR TO DELIVER NEW DRUGS?

For-profit firms do undertake early development of tropical disease drugs, albeit incidentally; they are also willing collaborators in efforts to manufacture approved drugs for distribution. However, firms are generally unwilling to bring even promising tropical disease drugs through clinical trials. Because clinical trials involve multiple stages of testing for drug safety and efficacy, they are expensive and time-consuming. For a blockbuster drug, the total cost for clinical trials can be hundreds of millions of dollars—a figure that represents the majority of the total cost to develop a new molecular entity. For tropical disease drugs, the total costs devoted to clinical trials may be somewhat lower. Still, these costs represent a significant portion of total development costs. Understandably, firms are willing to incur such costs only for drugs that have sufficient commercial promise. For tropical disease drugs, it has fallen to iOWH to serve as the missing link in the development process. But it is not clear whether for-profit firms can be persuaded to fill this void.

Insights from recent U.S. innovation policy offer a convenient point of reference. Early in the 1980s, patient groups lobbied for legislation to encourage for-profit firms to invest in developing drugs to treat rare diseases.[4] By definition, rare disease drugs have small commercial markets, so firms have little incentive to undertake their development. Indeed, before 1983, only 36 drugs had *ever* been approved in the U.S. to treat a rare disease.[5] Similar to the scenario for tropical disease drugs, pharmaceutical firms sometimes discover drugs that could potentially benefit rare disease populations—but they abandon their development because the drugs lacked another profitable application. This led Congress to pass the Orphan Drug Act of 1983 to encourage firms to develop rare disease drugs. The ODA contains two main incentives: a 50-percent tax credit on expenditures related to clinical trials for rare disease drugs, and a market exclusivity provision.

These two incentives—the push of tax credit and the pull of market exclusivity provision—were directed precisely at the stages of development that iOWH targets. In reality, the ODA offers only a weak incentive on the revenue side.[6] The marketing exclusivity provision is shallower than a patent in that it prevents com-

petitors from marketing the protected drug for only the same approved rare disease. Further, in 1991, the ODA was amended to include a clinical superiority provision, which is often interpreted as an incentive to give innovators a first-mover's advantage. However, the superiority provision is narrower than a patent in that it only applies if the second, competing, drug shares the same macromolecule with the first. In principle, this prevents competitors from making mere cosmetic changes to a drug, then marketing it for the same rare disease. Under the superiority provision, a competing firm can still market a different drug to treat the same rare disease, irrespective of clinical superiority. Also, a competing firm can still market a drug based on the same macromolecule to treat a second disease—something prohibited under a conventional patent. For all these reasons the ODA's impact on rare disease drug development rests less on the revenue side and mainly on the strength of the supply-side tax incentive.

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The ODA's tax incentive, however, has led to significantly more drugs to treat rare diseases.[7] Much of the ODA's impact is embodied in new clinical trials and the final development of existing drugs. Notably, for rare diseases with larger patient populations (and thus relatively larger commercial potential), the ODA has led not only to the final development of existing technologies, but also to the development of new technologies. Conversely, for the rare diseases with the smallest revenue potential, the ODA has had little impact on innovation. The differential impact of the ODA tax incentives is consistent with incentives that impact only the firms' revenue margins. Thus, even if a tax credit subsidized 100 percent of the development costs (that is, providing full cost recovery), it is unlikely that private firms would be induced to develop drugs with very small revenue potential; the rate of return to such an investment would still fall below the threshold hurdle rate. Stimulating private innovation in drug markets with low revenue potential requires incentives that impact revenue margins, not just cost margins. This principle remains true both for rare disease drugs that have high unit prices but low rates of use, and for drugs to treat tropical diseases that may affect more than half a million people, but people so poor that the firms have little hope of generating adequate revenue.

For markets with inherently small profit potential, the revenue-side incentives must be generated externally. Based on this principle, scholars suggest using purchase commitments.[8] However, any commitment, including an R&D prize or a purchase commitment, requires sources of non-market funding. In theory, countries afflicted by tropical diseases would internalize the economic returns from such drugs in the form of a healthier population. Therefore their governments should be willing to borrow against future returns in order to finance the R&D of specific tropical disease drugs. While a debt market currently exists in international development banking for developing infrastructure and providing health services, no such market exists to finance the uncertain R&D of tropical disease drugs.

Given this market failure, revenue-side policies must depend on investments that are generated externally: general tax revenues from wealthy nations, investments by international development and health agencies, or grant funding from private foundations. These are the same funding sources iOWH depends on for its drug development efforts. Ultimately, the development of tropical disease drugs requires external sources of finance to replace missing revenues, regardless of whether the enterprise performing the R&D is for-profit or non-profit. Compared to for-profit firms, iOWH may be better positioned to undertake tropical disease drug development for several reasons. As a non-profit, iOWH can raise capital more cheaply, and need not generate as high rates of return as a for-profit firm. However, its greatest advantage in raising capital may be its credibility. Innovation policies that reward a tremendously profitable industry for developing drugs that save the lives of millions of poor people may face stiff resistance in the court of public appeal. iOWH's greatest asset may be its credibility as a non-profit firm committed to improving global public health.

ARGUMENTS FOR GRANT AND AGENCY FUNDING

Governments of poor nations afflicted with tropical diseases have little ability to finance drug R&D by borrowing against future returns to health improvements. Funding for tropical disease drug development must come from wealthy nations—either through international agencies and foreign governments, or from private foundations. Several externalities justify, at least to some extent, the decisions of wealthy nations to make such investments. The one most frequently articulated is the communicable nature of certain infectious diseases. However, many of the deadliest diseases afflicting poor populations are tropical parasitic diseases that pose little risk to the populations in the temperate climates, or are bacterial diseases whose transmission is limited in wealthy nations that have well established public health infrastructures and relatively more robust populations.

A second common argument is that as a population becomes healthier, its worker productivity may improve, generating higher national income.[9] A country with a healthier and more stable labor force becomes both a stronger partner for foreign direct investment, and a more viable market for trade. A more tenuous extension of this argument suggests that the economic and political stability asso-

ciated with improved health may decrease discontent in poor nations, and increase internal stability of foreign states—outcomes that could reduce threats to domestic national security.[10]

No doubt some of those dedicated to improving global public health believe strongly in these arguments. Others are more strategic, using material or strategic arguments that governments and private foundations should make greater commitments, rather than stating the humanitarian arguments that motivate their own dedication to this effort. Indeed, the most significant argument for improving global public health may be the presence of fairness in our own utility function. Highly disproportionate amounts are invested in curing the diseases of developed nations while the citizens of poor nations experience enormous health disadvantages. This inequality makes many people uncomfortable. It is clear from Victoria Hale's account of founding iOWH that she and her dedicated staff are motivated by this very argument.

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If we avoid the humanitarian argument, and appeal only to material interests, our society runs a critical risk. The economic and strategic externalities may in fact not be that large. If and when it is established that these externalities are small, governments and international agencies may rapidly lose their political will to make larger commitments. If that happens, building the political will to reengage the same economic and political actors may be impossible in the short-run.

This risk is compounded by a second factor: trade-offs between economic and moral incentives. When we persistently couch the arguments for any action in a material framework, we run the risk of neglecting our moral impulses. An intriguing behavioral economic study found exactly this phenomenon, albeit in a smaller setting. Administrators of day-care center began charging a small financial penalty to parents who picked up their children late. In response, the parents' rates of late pick-ups *increased*.[11] If the researchers have correctly interpreted this behavior, then the financial penalty that the center charged was insufficient to alter parental behavior. Yet the mere fact of introducing the penalty effectively replaced the parents' moral incentive to be on time with the new financial incentive. Even worse, when the center removed the penalty system, the rates of late pick-ups did not decline to previous levels. Similar phenomena have been found in organizations that rely on altruism such as blood banks.[12] Appeals to material interests to support global health initiatives may replace more substantial moral and humanitarian sensibilities.

As it is, non-material externalities drive the objectives of the few private foundations and development agencies that provide a significant fraction of the drugs

for infectious and topical diseases. For example, in 2005 the Bill and Melinda Gates Foundation, "guided by the belief that all lives, no matter where they are lived, have equal value," committed $260 million in grants for malaria research—a decision that single-handedly increased the world's annual malaria research budget by 50 percent. This belief has also led the Gates Foundation to provide the vast majority of iOWH's funding. Eradicating some of the world's deadliest tropical diseases may therefore depend on funding obtained from an alarmingly small number of sources guided by humanitarian principles. This reality underscores the importance of investing R&D capital efficiently to have any hope of improving global public health. iOWH business model is built on this idea. By investing in existing drugs, it capitalizes off of R&D already performed by private pharmaceutical firms. Early iOWH successes promise future development of life-saving drugs. And fostering even greater collaboration between private firms and iOWH may ultimately save the lives of millions of people.

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