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# The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research

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## I. Executive Summary<sup>\*</sup>

**Introduction.** For the first time, there is a realistic prospect that rich nation governments and foundations will commit resources that are – just barely – adequate to fund neglected disease research. The challenge is to spend this money wisely. This paper stylizes existing proposals for how to fund research as “end-to-end” and “pay-as-you-go.” “End-to-end” models create a single reward to elicit discovery throughout the drug development pipeline. The leading end-to-end model, “AdvancedMarkets,” would use subsidies to boost the prices that LDCs pay for new drugs. AdvancedMarkets would reinvigorate incentives for private sector investment while leaving R&D decisions firmly in the private sector. The leading pay-as-you-go model, “Virtual Pharma,” would create the non-profit equivalent of private drugmakers. In this scenario, the public sector would retain control of R&D but outsource most of the work to private vendors.

**AdvancedMarkets or Virtual Pharma?** Funding agencies and governments (hereinafter “sponsors”) urgently need to know which solution can deliver new drugs at the lowest possible price. Success will require, in the gray language of business, cost containment. Because drug development entails roughly one dozen separate and distinct research tasks, cost-containment will require sponsors to accomplish two separate goals. First, a successful strategy must ensure that each research task is performed at the lowest possible cost. This will often mean outsourcing work to low cost providers. Second, it is not enough for R&D to be performed by the lowest cost providers. A successful strategy must also pass these savings on to sponsors.

AdvancedMarkets and Virtual Pharma both face significant challenges. There are at least three reasons to think that an AdvancedMarkets strategy would overpay for research:

- *Setting The Reward.* Sponsors know very little about commercial sector R&D costs. This means that sponsors who announce a guaranteed price will often overpay. This paper presents evidence suggesting that sponsors are likely to overpay by twenty to thirty percent on average.
- *Inefficiency in Outsourcing.* Commercial drugmakers face significant restrictions on their ability to outsource. First, fear of patent “piracy” may keep companies from outsourcing R&D to low cost Asian vendors. Second, drugmakers may be less able to work with open source groups and/or take advantage of their research. Both limitations will make commercial research and (eventually) manufacturing more expensive than it needs to be.

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<sup>\*</sup> The author thanks Andrew Farlow, Bronwyn Hall, Aiden Hollis, Victoria Hale, Jenny Lanjouw, Solomon Nwaka, Owen Barder, Arti Rai, Andrej Sali, Suzanne Scotchmer, and Tom Slezak for helpful discussions.

- *Mistrust of Sponsors.* Commercial firms may worry that sponsors will renege on their promises. If so, they will demand a higher reward to cover this risk.

The fact that AdvancedMarkets strategies face significant cost-containment penalties is not, by itself, dispositive. Virtual Pharma strategies also face significant challenges:

- *Inadequate Buying Power.* Publicly-funded Virtual Pharmas are unlikely to have the same purchasing power as large drugmakers. Hard bargaining, careful monitoring, and tactics like competitive bidding and coordinated purchases can reduce – but will not eliminate – this disadvantage. These purchasing power effects will be less significant to the extent that Virtual Pharma budgets approach spending levels found in private industry. This suggests that Virtual Pharma should become more efficient with scale.
- *Picking Winners.* Pay-as-you-go models like Virtual Pharma assume that non-profit organizations can pick winners at least as well as their commercial counterparts. While this assumption is plausible – particularly if Virtual Pharma executives are hired from private industry – it remains unproven. The principal uncertainty is whether foundations are prepared to fill the role of shareholders by ruthlessly de-funding inefficient ventures.

This paper argues that the foregoing drawbacks are generic and inescapable. Neither AdvancedMarkets nor Virtual Pharma is ever likely to be perfect. Instead, sponsors should choose whichever strategy is least imperfect. In principle, this decision is no different than the dollar-and-cents judgments that commercial businesses make every day. Cost – not ideology and sentiment – should be the determining factor.

**Designing Incentives: Beyond Patents.** Virtual Pharma strategies usually cost more when drug candidates are patented. This suggests that successful strategies should choose appropriate non-patent incentives for each step of the R&D process. Ultimately, each of these steps is unique and must be addressed on its own merits. Nevertheless, a few generalizations are possible:

*Basic Research.* Basic science requires intense individual creativity and the ability to combine and elicit knowledge from around the world. Grants are an appropriate incentive for meeting these social challenges.

*Early Phase Drug Discovery.* Early phase discovery translates basic research into ideas for curing disease and, eventually, specific chemical compounds (*i.e.*, “drug candidates”). Here, the dominant social challenges include persuading researchers to exercise creativity and eliciting knowledge that may be widely scattered around the world. Open source, prizes and (perhaps) grants are effective

mechanisms for meeting these challenges. Contract R&D and/or big science grants are an effective way to fund related chemistry research.

*Pre-Clinical and Clinical Testing.* The best way to decide whether a drug will work is to test it in cultures, animals, and ultimately humans. For this reason, researcher creativity and the ability to elicit widely-scattered knowledge have limited value once testing proceeds. Given that testing is extremely expensive, the dominant social challenge is cost containment. Contract R&D is particularly valuable in this environment because competition forces companies to offer the low prices.

*Manufacturing.* Contracts are also a powerful way to encourage price competition among manufacturers.

In many ways, the foregoing mechanisms resemble outsourcing strategies that commercial drugmakers already use to purchase R&D services today – and would presumably continue to use under an AdvancedMarkets system.

**The Way Forward.** So far, the debate over AdvancedMarkets and Virtual Pharma has focused almost entirely on theory. But theory without facts is indeterminate. In particular, it says nothing about which of the foregoing factors are most important. This knowledge will be vital if sponsors are to make a reasoned choice between AdvancedMarkets, Virtual Pharma, or some other strategy. This paper seeks to advance the discussion beyond theory by identifying – and in some cases starting to assess – the empirical evidence on which any rational decision must be based.

The fact that all available options have flaws should not dishearten us. Modern innovation economics teaches that there is no single “best” solution for every R&D problem. Instead, policymakers must always tailor solutions to individual challenges. The task now is to pick whichever institutions offer the best mix of strengths and weaknesses.

“Give us the tools, and we will finish the job.”

- Winston S. Churchill (1940)

## II. Introduction

Drug discovery for neglected diseases has reached a crossroads. For the first time, there is a realistic prospect that rich nation governments and foundations (collectively “sponsors”) will commit resources that are adequate – just barely – to fund drug development. The challenge is to spend this money wisely. Soon, sponsors must decide whether an end-to-end system like AdvancedMarkets, a pay-as-you-go system like Virtual Pharma, or some combination of the two is the best way to proceed. Given that every solution has drawbacks, theory alone is incapable of deciding the issue. Instead, policymakers must take stock of what is known and examine the evidence. This paper starts that process.

This paper takes the view that social institutions are tools like any other. Few of us are sentimental about which tools we use in everyday life. Success is the main – indeed, the only – criterion. Similarly, modern innovation economics teaches that no single R&D institution – be it patents, open source, or some other mechanism – is “better” than all the others. Rather, all institutions have inherent and unavoidable drawbacks. Given this fact, policymakers need to make careful judgments about which social problems are most urgent and then pick R&D institutions accordingly. This general strategy has several corollaries. First, policymakers must be careful to understand innovation problems before trying to solve them. Decisions must ultimately be based on evidence as much as theory. Second, it is not enough for critics to point out that a particular strategy has drawbacks. Given that every R&D institution is flawed, the best we can do is to choose our weak points carefully. Finally, hard choices are inevitable. No amount of discussion will produce an “ideal” solution and it is both pointless and irresponsible to wait for one.

Clear thinking requires explicit goals. This paper assumes that R&D budgets for neglected disease research will always be smaller than those for comparable rich nation diseases. For this reason, we define our principal goal, in the gray language of business, as cost containment. This goal is both widely shared<sup>1</sup> and justified by the budget projections cited in Section IV.A.1. Nevertheless, other goals may lead to other insights and recommendations. If so, analysts who adopt such goals should be equally explicit about what they are trying to achieve.

Section III (“Theory”) describes the generic strengths and weaknesses of different mechanisms including conventional patents, guaranteed purchase schemes, grants, open source, and contract research. It then addresses the further question of whether sponsors should fund drug development in stages (“pay-as-you-go” strategies) or create a single incentive (“end-to-end strategies) that leaves these decisions to the private sector. The goal is to explore the generic strengths and weaknesses of end-to-end and pay-as-you-go strategies without regard to the details of current proposals. Section IV describes the drug discovery R&D problem, estimated per-drug R&D costs, available R&D funds, and other facts needed to set policy. Section V (“Analysis”) builds on the preceding sections to examine specific proposals for organizing neglected disease research and proposes additional ones. Section VI (“Conclusion”) summarizes the main results of previous sections and makes concrete recommendations for moving forward.

## Nomenclature.

Proposals for funding neglected disease research often blend multiple strategies without quite realizing that they have done so. This blurring of concepts confuses the debate over neglected disease R&D. At the risk of adding to this confusion, we adopt the following definitions:

*End-to-End vs. Pay-As-You Go Solutions.* Successful drug discovery requires approximately one dozen separate and distinct innovation steps. We define “end-to-end” solutions as proposals that reward researchers after all of these steps are completed. We define “Pay-as-You Go-Solutions” as proposals that reward researchers at or near the time that each step is performed.

*Advanced Purchase Commitments and AdvancedMarkets.* Current proposals for end-to-end strategies usually rely on “Advanced Purchase Commitments” in which sponsors promise to purchase drugs or vaccines at a guaranteed price if R&D is successful. The Center for Global Development’s “AdvancedMarkets”<sup>\*</sup> proposal is the leading example of such a proposal.

*Virtual Pharma.* Following common commercial usage, we use this term to denote a drug development strategy in which a small management team acquires and monitors most of its R&D services from outside vendors.<sup>2</sup> Virtual Pharma is currently the leading model of a pay-as-you-go system.

*Strategic Investing.* We use this term to describe strategies in which sponsors subsidize private sector R&D programs (a) that would otherwise languish and/or be abandoned, and (b) nudge commercial programs toward the needs of LDCs.

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<sup>\*</sup>The Center for Global Development (“CGD”) reportedly plans to drop its “AdvancedMarkets” designation in favor of the more generic “APC.” Nevertheless, this paper retains the “AdvancedMarkets” designation, both because that is current usage and to avoid confusion with competing APC proposals by other authors.

*Access Strategies.* We use this term to describe strategies to ensure that drugs actually reach users.

*Private-Public Partnerships (“PPPs”).* We use this term generically to denote non-profit entities formed since the late 1990s to develop drugs. PPPs possess extensive drug development expertise. For this reason, they would probably play the role of Virtual Pharmas if a pay-as-you-go system were adopted. In the meantime, current PPPs often follow strategic investing models. Advocates of “hybrid” or “mixed” strategies argue that sponsors should fund PPPs *and* AdvancedMarkets incentives side-by-side.

*Sponsors.* We use this term to collectively describe rich nation governments, foundations, and other bodies who can, on the one hand, set incentives for developing new drugs or, on the other hand, purchase drugs or drug patents for neglected diseases. Except as otherwise noted, we assume that sponsors are concerned with cost, and do not otherwise have a preference between these two styles of procurement.

*Drugmakers.* We use this term to refer to commercial firms that currently develop and sell new drugs for rich nation diseases. Strategies for developing, manufacturing, and delivering new drugs to treat neglected diseases include incentives for drugmakers to participate in one or more of these activities.

“One should never believe any experiment until it has been confirmed by theory.”

- Arthur Eddington<sup>3</sup>

### III. Theory<sup>\*</sup>

Arguments over Advanced Markets and Virtual Pharma almost always focus on small details. This habit comes from policy discussions about rich nation diseases, where R&D institutions already work reasonably well. However, incremental tinkering is much less useful for neglected diseases, where the conventional incentive mechanism – patents – has failed. Here, policymakers face fundamental choices between radically different alternatives. Modern innovation economics teaches that all R&D institutions have generic strengths and weaknesses. If policymakers start by choosing the wrong institution, no amount of incremental tinkering is likely to save it.

This Section reviews R&D institutions. Section A (“Human vs. Scientific Frontiers”) sets the stage by reminding the reader that the social obstacles to R&D can be just as formidable as the scientific ones. Section B (“Comparing R&D Institutions”) compares the generic features of various well-known incentive systems including conventional patents, guaranteed purchase schemes, prizes, grants, open source, and contract research. Specialized features related to drug R&D are presented as necessary. Finally, Section C (“Grand Strategy”) examines how these incentives can be assembled into a coherent plan for accomplishing the dozen or so research steps that are needed to deliver drugs to market. Here, the main choice is between “End-to-End” proposals that establish a single reward for the entire R&D process and “Pay-As-You-Go” solutions that establish separate rewards for each sub-phase of development. Once again, we focus on generic strengths and weaknesses that transcend particular proposals.

#### A. Human vs. Scientific Frontiers

Human knowledge of biology is limited. For this reason, drug R&D is expensive and often fails. No social institution can change these facts. What social institutions can do is bring society closer to the limits set by human knowledge and available resources. Given that R&D can be done in theory, can we persuade flesh-and-blood workers to perform it?

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<sup>\*</sup>This Section, and the paper as a whole, owes a debt to Chapters 2 and 8 of Suzanne Scotchmer’s *Innovation and Incentives* (MIT Press 2004). Readers who seek a more rigorous presentation should consult that volume.

## B. Comparing R&D Institutions

Innovation economics teaches that no single R&D institution is the best solution for every R&D problem.\* It is therefore meaningless to ask, say, whether patents are better than open source or *vice versa*. The most we can do is assess the strengths and weaknesses of each institution against particular problems. All modern industrialized countries rely on a complex mix of patents, grants, prizes, in-house development, and contract research to promote innovation.

The social functions that any R&D system must perform are few in number. For purposes of this paper, we focus on the following:

**Efficient Access.** High prices (*e.g.* from patents) make drugs unaffordable to patients who would otherwise use them.

**Efficient Procurement.** New drugs should be developed at the lowest possible cost, particularly when this can be done without substantially delaying discovery.

**Agency Problems (Sponsors).** Researchers worry that sponsors may renege on agreements. For this reason, they will not perform projects unless they receive a premium that covers this risk. Sponsors can reduce such premiums – and hence, total R&D costs – by adopting commitment strategies (*e.g.*, signed contracts) that make it harder to renege. However, such strategies leave less flexibility to rearrange spending if and when circumstances change.

**Agency Problems: (Researchers).** Researchers may shirk, avoid, or overstate the value of their work. In each case, sponsors must pay more for the same amount of effort.

**Eliciting Information.** Many R&D problems make use of information that is scattered across the globe. This information can either be scientific (*e.g.* ideas for a new drug, knowledge of a critical gene sequence) or social (*e.g.* whether UNICEF would use a proposed drug if it existed). Sponsors can reduce researchers' R&D costs – and, indirectly, their own – by locating and delivering relevant information.

**Political Feasibility.** Different institutions face different political obstacles. At the most generic level, politics favors institutions that produce visible benefits, hide costs, and obscure responsibility for failure over those that do not. Some observers make the further claim that rich nation politicians have an inherent preference for strategies that involve patents (*e.g.* AdvancedMarkets) compared to

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\* This result makes innovation economics fundamentally different from classical microeconomics, which holds that markets provide a “dominant” solution to all but a handful of problems. Political rhetoric arguing that patents leave innovation “to the market” is confused on this point. As we shall see in Section II.B.2, markets for patented knowledge violate the assumptions on which microeconomic efficiency proofs are based.

strategies that do not (*e.g.*, Virtual Pharma).<sup>\*</sup> If these preferences lead politicians to fund patent-based solutions more generously than other alternatives, the cost-containment analysis presented in this paper could become irrelevant. For now, the political “boost” expected from patents (if it exists at all) is unclear. We ignore it in what follows.

This section summarizes the most important R&D institutions and describe the strengths and weaknesses of each. Our focus is deliberately generic. Specific proposals for organizing neglected disease research are deferred to Section V.

## 1. The Patent<sup>†</sup> System

Patent incentives have produced a torrent of new drugs over the past twenty-five years. However, fewer than one percent of those drugs address neglected disease.<sup>4</sup> As explained in Section IV.A.1, the reason is simple: Potential patent revenues from LDCs are much smaller than R&D costs. For this reason, all serious reform proposals require rich nations to fill this gap.<sup>5</sup> Despite this, conventional patents provide a useful a benchmark for judging other proposals. We therefore begin by describing how patent incentives produce cures for rich nation diseases.

**Description.** Patents provide the legal right to exclude competitors. Like any other power to exclude, the right permits owners to earn more profit than they could in a competitive market. Patent design features include “breadth” (*i.e.*, how different a competing product must be to avoid legal challenges), duration (*i.e.* when does the patent expire), and defenses and exemptions (*i.e.* when may third parties use the patent’s teachings without permission). Information that is not protected by patents is conventionally referred to as being in the public domain.

**Efficient Access.** When goods are expensive, consumers reduce consumption. In general, goods are efficiently produced and distributed when the cost of producing one additional copy equals the price that consumers are willing to pay for it. Since patents allow inventors to charge prices above marginal cost, protected markets are, by definition, inefficient. One complication is that sponsors may be both harmed and benefited by proprietary prices. Sponsors who develop drugs may benefit because proprietary prices replenish their R&D budgets. But sponsors who purchase drugs on behalf of patients will find their budgets stretched. [See Section IV.E].

**Eliciting Scientific Information.** Patent law encourages companies to hoard information until they can patent it. If firms hold different scientific knowledge and fail to share it, research in aggregate can be unnecessarily costly or misdirected.<sup>6</sup> In theory, parties can overcome this problem by writing contracts to share secrets. However, this

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<sup>\*</sup>The current popularity of patent-based institutions is anomalous. Historically, many societies have viewed patents more with suspicion than hope. For example, US Courts showed a marked antipathy to patents in 1880s, 1930s, and – to a lesser extent – the 1960s. Similarly, France showed a preference for prizes over patents in the late 18<sup>th</sup> and early 19<sup>th</sup> Centuries.

<sup>†</sup>For convenience, we use the term “patents” to include all forms of intellectual property.

may not be practical in cases where information may leak, contracting is expensive, or the parties are unaware of each other. Incomplete information forces up costs for companies performing R&D and – eventually – the sponsors who pay them.

**Eliciting Social Information.** Normally, patents provide a powerful market test of whether consumers think that an invention is useful. This protects society against spending money on trivial or ineffective products. Unfortunately, the market test for drugs is highly imperfect:

*Externalities.* Drug benefits are not limited to users. They also extend to family, care givers,<sup>7</sup> and people who might become infected if the disease is not treated.\* Public health authorities express this viewpoint when they stress that “We have to address populations . . . not [delivery] to patients but to populations.”<sup>8</sup>

*Agency Problems.* Consumers seldom pay for the drugs they consume. This encourages over-consumption. Conversely, physicians value some drugs less than their patients do.<sup>9</sup> This encourages under-consumption.

*Bounded Rationality.* Patients seldom have enough information to choose which drugs to consume. Furthermore, even physicians tend to avoid using new and unfamiliar drugs.<sup>10</sup> In theory, marketing campaigns can ameliorate this problem by providing information. In practice, skewed information may produce even more confusion and over-use.

*Market Power.* Large health care providers and government agencies frequently exert monopoly power on the purchasing side (“monopsony”) to drive down prices. In this case, patent revenues may understate a given drug’s value to society.

*Wealth Disparities.* Markets produce goods that users want and can pay for. Poor consumers have little or no voice in the market.

Given these imperfections, it is reasonable to think that public health authorities and other knowledgeable observers might be able to determine the value of new drugs more accurately than markets can. The truth of this assertion is an open question.

**Agency Problems (Sponsors).** An advantage of patents, at least in principle, is that the “sponsors” are consumers, who usually pay. The one caveat is that patent owners may have to enforce their patent rights against competing drug manufacturers in court. The prospect of costly litigation may deter R&D investment.

**Agency Problems (Researchers).** Patents face minimal agency problems on the researcher side because researchers must deliver and sell an actual product to receive their reward.

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\* For example, tuberculosis patients often stop taking drugs as soon as they feel better even though they pose a continuing risk to others.

**Efficient Procurement.** Patent owners have a legal right to prevent sponsors from developing drugs from protected compounds without permission. The patent owner will normally demand some form of compensation before it grants this permission. We return to this point below.

*Me-Too Drugs.* If the patent right is narrow,<sup>\*</sup> competition may reduce prices and increase access to drugs. In this case, patents will not harm access as much as is sometimes supposed. The narrowest patent that still elicits development occurs when the cost of inventing around the patent equals the first inventor's R&D costs. In this scenario, companies will continue to invent and patent competing products until patent owners earn just enough to cover their R&D costs.<sup>11</sup> This scenario is at least plausible for the pharmaceutical industry because (a) patent breadth is so narrow that even a slightly modified molecule may not be protected,<sup>12</sup> and (b) the risks and costs of taking such a "me-too" drug through the FDA approval process are roughly comparable to the pioneer product itself.<sup>†13</sup> Nevertheless, there are several reasons to think that patent revenues may still be significantly larger than R&D costs:

*Science:* The risk of failure is usually smaller for "me-too" compounds than for pioneer products.<sup>14</sup> On the other hand, the total number of "me-too" molecules capable of targeting a particular disease may be limited.<sup>15</sup> In the former case, revenues would be too low to cover R&D costs; in the latter case, too high.

*Market Imperfections.* There are many barriers to entry besides breadth. Examples include physician reluctance to adopt unfamiliar me-too drugs, state laws that limit pharmacists' ability to substitute generic drugs, bargaining power by HMOs and governments, and foreign cost controls or deliberate weakening of patent rights.<sup>16</sup>

Congress recognizes these effects and tries to compensate by tuning regulatory barriers to increase patent rewards for pioneer products.<sup>17</sup> Given that periodic adjustments can change the reward by ten percent or so,<sup>18</sup> it is reasonable to think that this process is fairly clumsy.

**Competing Away Profits.** A large patent reward may not benefit shareholders. Rational companies will continue to spend money competing with one another up to the expected value of whatever prize is posted.<sup>‡</sup> This competition may or may not yield benefits to patients. If the money is spent on R&D, companies may engage in *racing behavior* in order to be the first to file for patent protection. This behavior includes

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\* Rights are said to be "narrow" when even closely similar products do not infringe the patent.

†The argument is only true of so-called "compounds" patents. Patents based on "therapeutic mechanisms" are considerably broader. Congressional Budget Office, "How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry (1998), Chapter 3, p. 7 available at <http://www.cbo.gov/shodoc.cfm?index=655&dsequence=4>

‡For competitive markets, a profit-maximizing company will continue to invest in research as long as the expected reward exceeds the expected investment. The "expected reward" is defined as (total reward) x (probability of success).

mounting crash programs that deliver the drug sooner or funding parallel programs that insure against failure. Alternatively, companies may engage in forms of competition that add little or nothing to R&D. For example, they may spend money on patent litigation or marketing campaigns that yield little or no benefit to patients.

In practice, there is evidence that drug profits currently exceed normal economic returns by two to three percentage points.<sup>19</sup> This may indicate that competition has been at least partially suppressed. Alternatively, high returns could be caused by past errors in forecasting the costs and benefits of making R&D investments.

**Cumulative Innovation.** Firms that discover and patent new drug ideas often need partners to develop them. These partnerships usually take the form of license agreements in which the patent owner grants permission to develop its idea in return for royalties. For rich nation diseases, the partners are usually commercial firms. For neglected diseases, one of the parties may be a non-profit entity. Ideally, a patent system should allocate reward between the partners such that each partner covers its R&D costs. In practice, this goal is imperfectly realized although early negotiations usually produce better outcomes than late ones.

Consider first the case where both parties are commercial firms. Since each partner seeks to maximize profits, both have a shared interest in pricing their drug at high (technically: “monopoly” or “revenue maximizing”) prices. This gives both partners a larger “pie” to divide. The precise allocation depends on when the partnership is formed:

*Case 1: Parties Negotiate Before Second Partner Begins R&D.* If the patent owner is capable of developing the drug in-house, the parties will only form a partnership if the second party can develop the drug more cheaply. The parties will then allocate royalties in a way that splits these savings between them.

*Case 2: Parties Negotiate After All R&D Is Completed.* In some cases, the second company may develop a drug idea without knowing that patents cover it. If the patentee demands royalties after the drug has appeared on the market, the second developer can no longer threaten to withhold investment. This may lead to an allocation that does not cover the second developer’s R&D costs. For this reason, rational firms may decide not to enter a field where existing patent rights are unclear. This may occur, *inter alia*, where a plethora of patents exists (“patent thickets”) or where a promising compound’s mechanism is scientifically uncertain so that the developer cannot be sure which patented protein targets may be involved.

The principal lessons are that (a) mechanisms that identify owners of patents and facilitate early negotiations increase cumulative innovation, and (b) a large public domain creates a secure environment for would-be drug developers. Although we have focused on the case where the partners create a single drug, similar logic applies where the second

developer builds on an existing, first-generation drug to create a second-generation product.\*

The foregoing cases assume that both parties are commercial. The situation is different if one of the parties is a non-profit entity seeking to develop and then acquire new drugs at the lowest possible cost.† In this case, the parties must bargain over whether the finished drug will be sold at (a) the monopoly price, (b) marginal cost of manufacturing, or (c) some point in between. As before, the revenue split will be determined by bargaining. However, the non-profit partner will not agree to pay the commercial partner more revenues than it would cost to develop a competing, unpatented drug candidate from scratch. Strikingly, the existence of public domain drug candidates reduces the life cycle cost that sponsors must pay for *all* drugs, including patented ones.

**Political Feasibility.** Patents pay for innovation by imposing a hidden tax on each unit sold. However, most consumers seem unaware of this fact.<sup>20</sup> Where consumers do understand that a tax exists, they can seldom estimate its size. For this reason, politics tends to favor patents over other innovation incentives.

## 2. Boosted Demand.

Boosted demand strategies are based on the premise that rich nations can reinvigorate patent incentives by announcing an immediate and permanent increase in sponsor budgets to buy drugs for neglected disease.

**Efficient Pricing.** Larger budgets would make patent incentives viable. As noted above, patents lead to inefficient pricing.

**Agency Problems (Sponsors).** It is possible that commercial drugmakers would not respond to an initial funding increase, fearing that it would later be withdrawn. However, this is inconsistent with their experience in rich nations where budget increases, once implemented, are seldom withdrawn.

Commercial drugmakers might also fear that sponsors would exploit their buying power (“monopsony”) to drive down prices to unprofitable levels. Sponsors can gain credibility by demonstrating a *current* willingness to pay substantial prices.‡ They would

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\* The main difference is that revenues from the first generation product may not be large enough to justify first generation R&D. In this case, an efficient patent system must find a way to let the first generation developer share some fixed minimum share of second-generation royalties. This will not, in general, happen if (a) the first generation developer is incapable of developing the second generation product, and (b) the parties are unable to negotiate an agreement until *after* the first generation developer has completed its investment. Once again, early negotiations are more efficient than late ones.

† For the moment, we ignore hybrid models in which non-profit entities hope to earn patent revenues from rich nation markets and/or other sponsors.

‡ Significantly, it would be sufficient for a single well-funded sponsor to adopt the policy. The fact that US authorities are willing to pay “commercially reasonable” prices for pharmaceuticals supports worldwide discovery despite nearly universal free-riding abroad.

probably have to continue paying such prices long enough for political opponents to try (and fail) to reverse the policy. This might take a year or two.

**Agency Problems (Researchers).** As previously noted, patents are a reasonably effective method for minimizing agency problems on the researcher side.

**Eliciting Information.** As previously noted, patents are a reasonably effective method for eliciting scientific and economic information.

**Political Feasibility.** Boosted demand requires large, immediate spending increases. This makes it more visible – and less politically feasible – than schemes based on future payments.

**Comment.** Boosted demand will clearly work if the boost is large enough. This does not mean that it is efficient, since other mechanisms may be able to elicit development at lower cost.

### 3. Guaranteed Purchase Schemes

Guaranteed purchase schemes have been discussed more than any other proposal for organizing neglected disease research. The current Advanced Markets proposal builds on extensive earlier work by Profs. Kremer, Sachs, Maskus and others.<sup>21</sup>

**Description.** Conventional patents do not work in LDCs because consumers cannot pay the high prices needed to pay for R&D. Guaranteed purchase solutions supply this missing purchasing power by promising large co-payments.

**Efficient Procurement.** We have seen that “me-too drugs” can keep patented drug prices at or near per-drug R&D costs. Guaranteed purchase schemes have no comparable safeguard against overpayment. Instead, sponsors must guarantee a specific price in advance. In theory, sponsors can contain costs by specifying the lowest price that will still elicit innovation. In practice, this figure is highly uncertain. [Section III.B] For this reason, sponsors will almost always over- or under-pay by a substantial amount.

*Overpayment.* If sponsors set the price too high, the additional reward will be (a) competed away through “racing” behavior, (b) competed away through activities that add nothing to R&D (*e.g.* attempts to lobby prize committee members, regulatory bodies, and national legislatures), or (c) passed on to shareholders. To the extent that funds are diverted into channels (b) and (c), they generate no benefit for neglected disease research and are wasted. Funds spent on “racing” behavior will return some benefit by accelerating discovery and providing additional insurance against failure. Depending on technology, however, these benefits may be small. More importantly, a rational sponsor will normally have factored the desired level of “racing” behavior into its announced price. For this reason, any additional racing attributable to over-payment will normally

yield fewer benefits than the sponsor would have obtained by spending its money on other projects.\*

*Underpayment.* If sponsors set guaranteed prices too low, no R&D will occur. Prof. Kremer points out that this defect can be partially mitigated if sponsors are willing to announce guaranteed prices “at a relatively modest level” and slowly raise them over time. However, sponsors cannot raise the reward faster than interest rates. If they do, companies will simply defer R&D in hopes that rewards will increase still further.<sup>22</sup> In practice, the effectiveness of this strategy is limited by two factors:

*Imperfect Knowledge of Actual Costs.* As explained in Section IV.B, per-drug R&D costs are uncertain by approximately fifty percent. Assuming ten percent interest rates (compounded annually), an optimistic sponsor who starts at the lower figure might have to raise the reward for eight years before it became effective.

*Growth of Actual Costs.* If real R&D costs grow faster than interest rates, the reward never elicits development. If real per-drug R&D costs only grow at five percent *per annum*, an optimistic sponsor who starts at the lower price might have to raise the reward for fifteen years before it became effective.

An initiative that includes decades-long delays is less valuable than one that begins immediately. Furthermore, there are political limits to how long a program can persist without delivering results. For these reasons, guaranteed purchase solutions will likely start at some intermediate price and sweep upward, trading higher prices for shorter time frames in expectation.

**Eliciting Information.** Competitors in guaranteed purchase systems face the same incentives to hoard or share information as they would in the conventional patent system.

**Agency Problems (Sponsor).** Guaranteed purchase systems require sponsors to pay out rewards *after* researchers have delivered the innovation. This creates an incentive for sponsors to renege. The simplest and in many ways most effective solution is to specify what contestants must accomplish in clear, judicially enforceable rules.

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\* AdvancedMarkets proponents frequently argue that sponsors only have to set rewards “high enough to accelerate research and development” but low enough so that “sponsors do not commit themselves to paying more for the vaccine than it is worth to society.” According to this criterion, sponsors can choose from a relatively “large window” of acceptable vaccine prices. AdvancedMarkets Working Group, *Making Markets for Vaccines: A Practical Plan to Spark Innovation for Global Health*, (Center for Global Development & Global Health Policy Research Network: (Consultation Draft 2004) at p. 53. As explained above, this criterion only says that the AdvancedMarkets is better than doing nothing. It does not say whether the same funds would have been better spent on other projects. Furthermore, vaccines have unusually high social value. The AdvancedMarkets “window” will normally be narrower for drugs and medical devices.

The price of judicially enforceable rules is flexibility. Even if rewards are rational *ex ante*, changes in science, LDC health needs, and funding are certain to render rewards too high or too low *ex post*. It is tempting to fix this problem by giving sponsors discretion to adjust prices upward or even downward. Absent objective data on R&D costs, however, there is no natural way to constrain this discretion. For this reason, researchers will normally demand a large premium before participating in such a system.

**Agency Problems (Researchers).** In general, agency problems among researchers are minimal because – as with patents – payment follows delivery. However, if sponsors have discretion to change the reward, researchers may misrepresent their costs, the probable value of their research, or make strategic decisions to withhold research until the guaranteed price has risen.

**Cumulative Innovation.** The challenge of choosing an appropriate guaranteed price is compounded for improved, second-generation drugs, whose R&D costs are likely to be even more speculative than those of first-generation products. In general, however, sponsors should offer a lower reward for second-generation drugs than for first generation products. There are two reasons for this:

*Less Value.* Assuming that first generation drugs work reasonably well, the incremental value of a second generation drug is likely to be smaller;\* and

*Lower R&D Costs.* Some – but not all – second-generation drugs may cost less to the extent that they build on first generation discoveries.

Declining rewards can be implemented in a variety of ways including (a) allowing a prize committee to adjust rewards based on incremental improvement, and (b) limiting rewards to a fixed number of doses, so that second generation drugs arrive after most of the reward has been collected.

As explained in Section III.B.2, an effective incentive system should distribute rewards that are large enough to cover each generation of inventors' R&D costs. Most guaranteed purchase schemes require would-be drug developers to declare their existence. This facilitates early license negotiations. In this sense, guaranteed purchase solutions may be more efficient than conventional patents.

**Political Feasibility.** Guaranteed purchase programs are less politically favored than patents, since co-payments (a) must be promised in advance and (b) are likely to be highly visible when made. These effects are somewhat mitigated by the fact that co-payments are deferred and spread over a period of years.

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\*The situation for vaccines is slightly more complicated. Each time an individual is vaccinated, the incremental value of vaccinating other individuals declines. This is true whether or not second generation vaccines are eventually developed.

### 3. Prizes

**Description.** Governments have offered innovation prizes since ancient times.<sup>23</sup> In what follows, we distinguish between “targeted” and “blue sky” prizes. The former specify a particular problem and, in some cases, generalized approaches for solving it. By contrast, blue-sky prizes give contestants broad freedom to choose solutions and even problems. Contestants who produce the most valuable research receive a reward. The challenges that prize designers face often depend on where a project falls along the continuum between targeted and blue sky prizes.

**Efficient Access.** Prizes reward researchers once; thereafter, the knowledge is available to everyone at zero cost.\* This eliminates the inefficient pricing associated with patents.

**Efficient Procurement.** Prize systems require sponsors to choose the amount of the researcher’s reward. Unlike patents – in which researchers can never receive a greater reward than consumers are willing to pay – there is no limit to the potential overpayments associated with prizes.

**Agency Problems (Sponsors).** Many prizes depend on clear rules (*e.g.*, the “fastest airplane,” “first man to fly across the Atlantic”) that can be readily enforced in court.\* Sometimes, however, a prize’s greatest strength may be its capacity to elicit innovative solutions to existing problems or solve problems that the sponsor was unaware of. In this case, the sponsor cannot specify clear rules in advance, which creates an agency problem.

Where clear rules are not feasible, sponsors can still minimize agency problems by adopting commitment strategies that limit their ability to renege. For example, sweepstakes frequently promise that “all prizes will be awarded.” Absent evidence that the sponsor favors one contestant over another, such promises provide a powerful assurance that the best research will be rewarded. As with guaranteed purchase schemes, such strategies limit the sponsor’s flexibility to reallocate resources if conditions change. For example, if unforeseen scientific barriers make drug development unexpectedly difficult, sponsors must award the prize even if only trivial drugs are delivered. Prizes can also be designed to include market-like tests of value. In Eighteenth Century France, for instance, sponsors rewarded inventors with sliding scale prizes based on how many factories adopted their machinery.<sup>24</sup>

**Agency Problems (Researchers).** Like patents, prizes for finished drugs entail minimal agency problems because researchers must deliver a product to earn their reward. However, if prizes reward intermediate progress whose ultimate value is unknown, researchers may have strong incentives to overstate the value of their work.

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\* We assume that the sponsor requires prize recipients to donate their inventions to the public.

\* *Himfar v. United States*, 355 F.2d 606 (Ct. Cl. 1966) (US could not renege on unilateral promise to purchase domestic manganese ore at predetermined prices). In many cases, prizes are more enforceable than patent rights.

**Eliciting Information.** All prizes elicit information from contestants. However, the amount of information is very different depending on whether the prize seeks “blue sky” ideas or solutions to a “targeted” problem. “Blue sky” prizes may not be necessary where sponsors already have information about the best way to proceed. In this case, “targeted prizes” – which feature clear rules and therefore limited agency problems – are usually more cost-effective.

**Relation to Patents.** Profit-maximizing firms ignore prizes whenever patents offer a greater reward. This does not significantly constrain prizes for neglected disease drugs, since patent rewards are (by hypothesis) inadequate. Sponsors can set prizes that are only slightly larger than expected R&D costs.

**Political Feasibility.** Prize payments tend to be more visible than patent revenues and are, to that extent, politically disfavored. Despite this, recent prizes by DARPA<sup>25</sup> and NASA<sup>26</sup> show that this mechanism is politically feasible.

## 4. Contract Research

**Description.** The most obvious way to obtain R&D is to purchase it. Government research frequently relies on contract research, particularly for military and aerospace procurement. Success stories like the Polaris and Apollo programs show that contract research can be extremely effective.

**Efficient Procurement.** Unlike prizes, sponsors can use contracts to obtain information about vendors’ R&D costs. Sponsors can do this by comparing vendors’ prices or, more formally, by soliciting sealed bids. In either case, the winning vendor’s price will normally be (a) higher than its own R&D costs, but (b) lower than the R&D costs of its next nearest competitor. Within this range, the exact price depends on bargaining between the parties.

Patent law short-circuits competition by preventing the sponsor from outsourcing without the patent owner’s permission. Although the patent holder may agree to outsource research, it will normally extract a monopoly price for doing so. However, as previously noted, public domain drug candidates limit the price that patent owners can extract.

**Agency Problems (Sponsors).** Research contracts are enforceable in court. While this process is far from perfect, it is probably no worse than for other commercial agreements. Contracts that provide for frequent progress payments can reduce agency problems on the sponsor’s side still further. However, this comes at the cost of increased agency problems on the researcher side (see below).

**Agency Problems (Researchers).** Contract research gives developers “incentive[s] to inflate . . . R&D cost,”<sup>27</sup> to overstate results in order to keep revenues

flowing past the point when projects should be terminated, and to shirk work that has previously been promised. The significance of these drawbacks depends on sponsors' ability to monitor and punish cheating. All else being equal, contracts that involve standard labor operations (*e.g.* drawing blood and performing lab tests at regular intervals) will have fewer problems than those that require discretion or creativity (*e.g.* inventing a "better" drug). There are also tradeoffs in how well contracts control agency problems as between researchers and sponsors. For example, a contract that provides for progress payments at long intervals gives sponsors more opportunities to detect and punish cheating but also makes it easier for sponsors to renege.

Sponsors with substantial purchasing power often have more power to control agency problems. If researchers believe that repeat transactions are likely to be large and significant, they will work hard to keep the sponsor's business. This suggests that large sponsors face fewer agency problems than small ones.

**Eliciting Information.** Sponsors normally decide what R&D to purchase without seeking input from vendors. In this case, contract research does little or nothing to elicit information. However, this limitation is not fundamental. For example, the US Pentagon frequently invites vendors to submit competing proposals. In this case, the winning bid usually depends on a mixture of price and performance. The system resembles a prize, since cost-containment tends to be less effective than it would be if vendors offered bids to build a pre-defined product.<sup>28</sup>

## 5. Grants.

**Description.** Grants typically pay for work in advance based on the recipient's promise to perform. Recipients have an incentive to perform because broken promises reduce their chance of receiving similar grants in the future. This somewhat improbable scheme routinely produces world-class science.

Fear of losing future grants works less well for large science collaborations where (a) budgets are large, (b) results are infrequent, and (c) large teams (100+ members) make responsibility diffuse. Modern "Big Science" programs reduce these risks by giving a small group of principal investigators the power to allocate funds within the collaboration. In effect, sponsors delegate enforcement to individual leaders who are better placed to monitor and de-fund non-performing researchers. Meanwhile, the leaders themselves remain accountable to sponsors.

**Efficient Procurement.** Grant proposals provide little cost containment beyond an implicit assurance that promised research results will generate sufficient benefits to cover the cost of any sums invested. Since grants reward the best idea, no effort is made to find the lowest cost researcher. If ideas are scarce, that may be an acceptable tradeoff.

**Agency Problems (Sponsors).** Researchers usually receive funds before they begin work, obviating agency problems on the sponsor side. Grants paid over multi-year periods produce greater uncertainty.

**Agency Problems (Researchers).** Commentators sometimes argue that grants give scientists incentives to portray research opportunities favorably, stray from the task, prepare the next application, or work on unrelated projects.<sup>29</sup> However, these criticisms ignore the fact that researchers who fail to reform may not receive grants in the future. Simple models suggest that agency problems on the part of researchers are intermediate between those posed by patents and contracts. Interestingly, the waste of funds may grow in proportion to the size of sponsors' grant budgets.<sup>30</sup>

**Eliciting Information.** Because grants are awarded competitively, there may be a powerful short-term incentive for researchers to suppress result in order to avoid empowering rivals. In the long run, researchers must prove to grant agencies that their work has yielded benefits. This provides a powerful incentive for publication over time scales comparable to the grant cycle itself.

## 6. Open Source.

**Description.** Open source software collaborations show that it is possible to produce complex products like computer programs without patents. Participants frequently join collaborations for non-monetary incentives including ideology, a desire to make products for their own use, a desire to learn about programming, to gain reputation, or to advertise skills to potential employers. Empirically, the success of projects like LINUX shows that these seemingly disparate incentives sometimes generate impressive amounts of labor. However, these incentives are markedly less successful at supplying capital and materials. This gap is partially filled by corporations that support open source projects in order to sell complementary goods (*e.g.*, service, hardware), persuade consumers that software will continue to be supported, and/or to persuade consumers that prices will not rise in the future.

The foregoing discussion suggests that open source methods work best for information goods that require large amounts of labor but relatively little capital or materials. This explains why existing open source projects almost always involve software.\* However, certain segments of the drug discovery “pipeline” also require relatively little capital or materials. [*See*, Section IV.C] It is therefore natural to ask whether open source methods can be extended to drug discovery.

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\*Eric von Hippel has emphasized that the association between open source and software should not be exaggerated. Even in the “old economy,” companies that developed ideas in-house often traded information without bothering to patent it. The resulting innovation networks were functionally indistinguishable from modern open source. Eric von Hippel, “Open Source Software Projects as User Innovation Networks” (2002), available at [http://www.idei.fr/doc/conf/sic/papers\\_2002/vonhippel.pdf](http://www.idei.fr/doc/conf/sic/papers_2002/vonhippel.pdf). Indeed, one can argue open source production goes back to the *Iliad*, in which balladeers created, extended, and improved a shared product. According to this argument, the quality of Homeric literature owes a debt to the “many eyeballs” of audiences and bards who found and corrected flaws over the centuries.

**Efficient Pricing.** In theory, open source collaborations could patent their products and divide the proceeds. In practice, collaborations usually distribute their products free-of-charge, as is efficient.

**Efficient Procurement.** Subsequent innovators are normally free to extend open source results without charge. This promotes efficient procurement. Open source licenses (*e.g.*, “GPL”) that limit users’ ability to modify and extend software reduce the efficiency of this model, although the size of this effect is unclear.\*

**Agency Problems (Sponsor).** Many open source collaborations have no outside sponsor. When sponsors do exist, they usually provide support in small, day-to-day increments. In either case, there is relatively little potential for sponsors to renege.

**Agency Problem (Researcher).** The absence of outside sponsors limits open source workers’ incentives to misappropriate funds, avoid work, or misstate their results. Nevertheless, a few open source motivations (*e.g.* reputation) may create incentives to overstate work or claim credit due to others.

**Eliciting Information.** The patent system uses markets to tell researchers which products to build. Open source volunteers, by contrast, are often driven by motives (*e.g.* education, reputation) that often have little or nothing to do with consumer preferences. This suggests that open source collaborations may be less likely to know, let alone develop, products that consumers want. Similarly, open source incentives do not grow with consumer demand. In the patent system, potential rewards are bounded only by consumers’ ability to pay. By contrast, open source volunteers have a fixed appetite for incentives like “reputation” or “education.”

**Political Feasibility.** Open source approaches are politically favored because they depend on volunteer labor (and, sometimes, corporate contributions) instead of tax dollars.

## 7. Strategic Investments.

**Description.** Strategic investing refers to strategies in which sponsors offer cash or in-kind subsidies to commercial R&D programs that are languishing or about to fail. The power of such strategies depends on finding projects where relatively small amounts of public money can persuade private drugmakers to continue investing in otherwise marginal projects.

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\*In some cases, contract restrictions may be needed (a) to keep companies from “capturing” products by creating patented versions that draw users away from the original product which is then abandoned, and (b) to block a “prisoner’s dilemma” dynamics in which individual collaborators patent their contributions even though they would be better off if everyone refrained from such behavior. A. Gambardella & B. Hall, “Proprietary vs. Public Domain Licensing of Software and Research Products” (2004), available at [emlab.berkeley.edu/users/bhhall/papers/GambHall04\\_RP.pdf](http://emlab.berkeley.edu/users/bhhall/papers/GambHall04_RP.pdf)

**Efficient Procurement.** In general, the private partner will own patents on the idea to be developed. For reasons discussed in Section III.B.2, the amount that the non-profit partner pays will (a) include some payment to the patent owner over and above its expected R&D costs, but (b) be less than what it would cost the sponsors to develop a comparable drug candidate from ideas in the public domain. In practice, the patent owner may also extract larger subsidies by exaggerating its expected R&D costs (*see* below).

**Agency Problems (Sponsor).** Sponsor agreements are normally enforceable in court. However, an insolvent sponsor may not be able to pay if a judgment is rendered. While insolvency is seldom an issue for short-term projects, sponsor funding can be highly uncertain for projects that last more than a few years. Companies will normally require a premium to cover the risk that sponsors may fail to meet their commitments.

**Agency Problems (Researcher).** Rational companies seek to create products that will earn maximal profits at the lowest possible R&D cost. This creates several potential agency problems:

*Crowding Out.* Companies have an incentive to exaggerate the need for subsidies and to reduce their own investment as far as possible. This leads to a crowding out dynamic in which public money displaces private funds with little or no net increase in spending. This problem is significant for strategic investment models, since sponsors are seldom able to check researchers' assertions that projects would be delayed or abandoned in the absence of subsidies.

*Research Direction.* Commercial drugs are typically most profitable when they are optimized for rich nation consumers (*e.g.* soldiers, ecotourists) whose needs may be very different from those of LDCs. Companies have an incentive (a) to exaggerate the expected usefulness of new drugs to patients living in LDCs, and (b) to make subtle research choices that reduce this usefulness still further.

*Overstating Results.* Researchers have a strong incentive to overstate progress in order to maintain, and if possible increase the flow of subsidies.

*Reduced Effort.* Researchers may be able to earn a profit from sponsor subsidies whether or not a product is eventually delivered. At this point, they may start to avoid work, particularly if they have private information suggesting that the project is likely to fail.

**Eliciting Information.** By definition, subsidies override market signals. Sponsors should be skeptical of the notion that they possess better information about the scientific worth and/or market viability of drug candidates than private companies do. Despite this, there are several reasons why strategic investment might make sense:

*Non-Market Values.* Markets deliver goods based on consumers' ability to pay. However, society routinely overrides this judgment so that the poor can obtain "essential" goods. Subsidies are one means of doing this.

*Correcting Market Imperfections.* Sponsors may believe that they have greater knowledge of scientific, regulatory, or commercial opportunities than the market itself does. While there is no reason to think that sponsors have superior information with respect to the first two categories, they may have superior information about public sponsors' willingness to buy new drugs if R&D succeeds.

**Targeted Tax Credits.** Commentators sometimes propose using targeted tax credits to subsidize companies developing drugs for malaria, tuberculosis, and HIV. In addition to the normal problems of subsidies recounted above, tax credits face two additional hurdles:

*Agency Problems.* Creative accounting could divert credits into activities that are only tangentially related to neglected disease R&D. Furthermore, R&D would usually be optimized for commercial markets rather than LDCs. Restricting tax credits to clinical trials in LDCs would ameliorate these problems for late stage R&D.<sup>31</sup>

*Efficient Procurement.* Credits would be useless to biotech firms (which seldom have current income) unless they were tradable. But in this case, trading partners would insist on receiving part of the tax benefits. Prof. Kremer estimates that this would reduce the value of any credits by roughly five percent.<sup>32</sup>

**Government Equity Investments.** Prof. Kremer argues that public sector equity investment is similar to direct subsidies, but "somewhat exacerbated since firms with marginal ideas have a greater incentive to seek government investment while firms with good ideas prefer to keep their equity undiluted."<sup>33</sup>

**Political Feasibility.** Subsidy payments typically have low visibility, except to the recipient. This may create a dynamic in which recipients use political pressure to preserve programs that are no longer justified on scientific grounds.<sup>34</sup>

## 8. Patent Buyouts.

**Description.** A patent buyout refers to a transaction in which a sponsor purchases a drug patent from a commercial drugmaker and puts the resulting information in the public domain so that the drug can be produced and distributed at a competitive price. This solves the inefficient pricing normally associated with patents. However, the problem of setting a buyout price is just as difficult as setting a prize.

**Efficient Procurement.** To elicit investment in the drug, the buyout price (like a prize) must be greater than the R&D cost, and to be efficient for the sponsor it must be close to the R&D cost. In order to set a buyout price, Prof. Kremer has proposed a

technique to estimate social value from the commercial value.\* However, this technique is not sensible for LDCs where social value is taken as users' willingness to pay. The victims of neglected disease typically have very little willingness to pay because they have very little ability to pay. That is the whole problem.

**Agency Problems (Sponsors).** If buyouts are mandatory, sponsors have a strong incentive to pay too little for the patent. In principle, this problem can be alleviated by allowing courts or other neutral bodies to determine payment size. While this procedure works reasonably well in US eminent domain proceedings, the process remains highly expensive and uncertain. Researchers will normally demand a premium to cover these risks.

**Agency Problems (Researchers).** If buyouts are voluntary, researchers have a strong incentive to overstate the value of their research.<sup>35</sup>

**Market Imperfections.** The fact that sponsors have placed the *legal* right to manufacture drugs in the public domain does not guarantee that companies will actually do so. If the minimum efficient scale for manufacturing is comparable to the size of the worldwide market, the first company to develop a drug will normally remain a *de facto* monopolist even after a buyout.<sup>36</sup> In this case, a buyout would waste sponsor's resources without reducing the price to users.

**Political Feasibility.** Like any lump-sum payment, the main political objection to patent buyouts is their visibility. For this reason, sponsors and recipients may be criticized more than if the patent were left in place so that payments were spread over millions of doses. In the highly regulated drug market, authorities could respond to the perceived windfall of a buyout with confiscatory taxation, hard bargaining on unrelated transactions, or price regulation.<sup>37</sup>

## 9. Transferable Intellectual Property Rights (“TIPRs”).

**Description.** Some commentators argue that drugmakers who develop cures for neglected disease should be rewarded with extensions on their existing patents for unrelated, rich nation diseases. By definition, such schemes tax a small and essentially random group – users to rich nation pharmaceuticals – to support neglected disease research.<sup>†</sup> We ignore this fairness issue in what follows.

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\* Prof. Kremer has suggested an ingenious scheme for eliminating the foregoing agency problems for rich nation markets. Under his proposal, authorities would invite companies to bid for the right to own and exploit particular patents. Government administrators would pay an estimate of social value to the inventor based on the winning bid, and then dedicate the patent to the public domain, or (b) sell the patent to the winning bidder at the agreed price. Outcome (a) is selected 999 times out of 1,000. When this happens, the patent is dedicated to the public so that no would-be user is priced out of the market. Outcome (b) is only selected once out of every 1,000 times. Because there is some chance that companies will actually purchase the patent at the bid price, they tender bids that accurately reflect their sometimes privately-held knowledge of potential market value.

<sup>†</sup> Equivalent schemes for encouraging commercial R&D into bioweapons vaccines are often referred to as “wild card” incentives. See, e.g., Divis, Dee Anne, “BioWar: ‘Wild Card’ Patent in Bioshield 2,”

**Inefficient Procurement.** Because companies with the best ideas for neglected disease research seldom own blockbuster patents, TIPRs would almost certainly have to be tradable.<sup>38</sup> This leads to two problems. First, companies would extend the life of the most lucrative patents – *i.e.*, the patents that would benefit rich nation consumers most if they were allowed to expire. This is not necessarily a disadvantage for LDCs, since it implies a larger reward for neglected disease research. It would, however, aggravate Efficient Access problems for rich nation consumers. Second, firms that participated in the trades would insist on a share of the reward.<sup>39</sup> This means that only part of the tax incentive would be available to elicit new R&D.

**Eliciting Information.** Sponsors would have to decide whether each new drug for neglected diseases was worthy of reward. Patents would no longer provide a market test of value<sup>40</sup>

**Political Feasibility.** The hidden tax imposed by patents is less visible than explicit prize and, to that extent, might be politically easier.<sup>41</sup> However, the scheme would require extensive legal and political groundwork.<sup>42</sup> Some US cases seem to suggest that TIPR legislation would be unconstitutional.<sup>43</sup>

## C. Grand Strategy

So far, this paper has focused on incentive institutions. However, policymakers face a second choice. As described in Section IV.C, drug development can be visualized *either* as a single monolithic inquiry *or* as a series of roughly one dozen separate and distinct subtasks. Sponsors who choose to treat drug development monolithically must design a single incentive that elicits development at every stage of the drug development pipeline. We refer to such incentives as “end-to-end” rewards in what follows. Conversely, sponsors who choose to manage each individual stage of the drug development process must design separate incentives for each. Because sponsors must pay out rewards continually, we refer to such systems as “pay-as-you-go” proposals.

This section compares the generic strengths of “end-to-end” and “pay-as-you-go” proposals while deferring discussion of specific proposals (*e.g.* AdvancedMarkets) to Section V. As always, we ask which class of proposals is most likely to contain costs.

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*Washington Times* (Sept. 1, 2004) available at <http://www.washtimes.com/upi-breaking/20040901-084333-2886r.htm>.

## 1. “End-to-End” Solutions.

**Description.** End-to-End solutions mimic patent incentives by offering a single, large reward to companies that successfully complete the R&D process. This imposes two stringent requirements not found in competing, pay-as-you-go schemes. First, sponsors must select a single reward that is large enough to cover researchers’ expected costs over the entire R&D cycle. Since drugmaker costs are poorly known, the amount of this reward will usually reflect substantial guesswork. Second, sponsors must withhold the reward until the entire R&D process has been completed. In practice, this may take twelve to fifteen years. We examine each of these issues in turn.

**Setting the Reward: Efficient Procurement.** Deferring the reward until the end of the R&D cycle removes the public sector’s ability to manage R&D at each separate stage of the drug discovery process. Instead, the task is left to private drugmakers. This is only an advantage if commercial drugmakers are more competent than PPPs. We return to this point in Section V.C.

Significantly, end-to-end solutions *do not* prevent outsourcing. Indeed, commercial drugmakers can be expected to outsource R&D whenever it is cost-effective to do so. From the sponsor’s standpoint, procurement will only be efficient if (a) the sponsor pays minimal markups for outsourced work, and (b) the drugmaker outsources its research to the lowest cost vendor. We consider these factors in turn.

*Overpaying the Drugmaker.* Practically all proposed end-to-end solutions involve patents, guaranteed purchases, prizes, and other incentives that require sponsors to estimate researchers’ R&D costs in advance.\* As previously noted, these estimates are highly uncertain. If sponsors guess too low, no R&D will be elicited. If sponsors guess too high, substantial overpayments are likely. In practice, sponsors must also trade the likelihood of overpayment against the probability of failure. For example, suppose that there is a 75% chance that per drug R&D costs fall between \$800 and \$900 million. In that case, a sponsor willing to tolerate a one-in-eight chance that research would not go forward would set a prize equal to \$900 million. Assuming for simplicity that drug costs within the quoted range were evenly distributed, the sponsor would on average overpay by \$50 million.†

*Ability to Outsource.* Even if the sponsor chooses a single, end-to-end incentive this does not end the inquiry. Companies competing for the reward will still outsource work if they can save R&D costs by doing so. As explained in Section IV.C, outsourcing is ubiquitous in modern drug discovery. This strongly suggests that outsourced research is competitive with, and may often be more cost-effective than, traditional in-house R&D programs.

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\* One can imagine a system where companies bid for the right to perform contract research. Such a system would constrain initial bid prices, although researchers would still have an incentive to overstate and prolong work once the contract was signed.

† We assume that nothing is known about the distribution of costs outside the \$800 - \$900 million window.

In theory, a profit-maximizing commercial drugmaker should (a) always outsource individual research steps to the lowest cost vendor, and (b) choose whatever innovation institution (*e.g.*, contracts, prizes, open source) is likely to be most cost-effective. In practice, commercial drugmakers may not be able to reach this goal. Constraints include:

*IP Barriers.* Section IV.C presents evidence that drugmakers avoid outsourcing research to vendors and/or countries with a history of patent infringement. Anecdotal evidence suggests that many otherwise desirable low cost vendors fall in this category.

*Institutional Barriers.* Drugmakers are not strict profit-maximizers. Companies may face institutional pressures to keep R&D in-house even when outside vendors could do the job more cheaply.

*Ideology.* Some, but not all, open source volunteers are hostile to commercial development. Non-profit entities may be able to enlist these volunteers more efficiently than commercial drugmakers can.

*Secrecy.* R&D programs are more efficient when companies share information. In principle, sharing can proceed despite trade secrets and patents so long as companies are able to buy and sell information. In practice, such transactions may be difficult or impossible to consummate if firms (a) do not know which competitors possess relevant information, or (b) cannot demonstrate that their information has value without revealing it. Information sharing may also be limited by the transaction cost of negotiating and drafting agreements. If this happens, firms will inefficiently duplicate research.<sup>44</sup> Anecdotal evidence suggests that excessive secrecy does indeed make commercial neglected disease R&D less efficient.<sup>45</sup>

Based on the foregoing discussion, end-to-end systems may make outsourcing significantly harder. The importance of this effect will, in general, depend on the extent to which outside vendors offer significant cost advantages over in-house development.

**Effects of a Delayed Reward.** As previously noted, end-to-end rewards are frequently withheld for more than a decade. This produces severe agency problems on the sponsor side. Incentives can also be undercut if drugmakers are allowed to compete *after* their R&D programs are complete (the “two-stage game” problem). We examine each of these issues in turn.

*Agency Problems (Sponsors).* Sponsors are more likely to renege where the promised reward is (a) large, and (b) not payable until contestants have sunk substantial R&D costs. By definition, these problems tend to be larger for end-to-end solutions than for pay-as-you go systems in which rewards are divided into multiple payments spread over time. In practice, designers of end-to-end solutions must (a) pay a premium to cover the danger that sponsors will renege, (b) adopt commitment strategies that make renegeing

less likely, or (c) adopt some combination of the foregoing. All three options will usually add to cost. For example, strong commitment strategies make it very unlikely that sponsors can adjust rewards downward if unforeseen changes in technology reduce the per-drug costs of R&D.<sup>46</sup> Since drug development typically takes a decade or more, these effects are almost certainly significant.

*The Two-Stage Game Problem.* Systems that award prizes *after* R&D is complete run the risk that companies will have to compete twice – Once at the R&D stage and again after their drugs have reached the market. Such two-stage games are catastrophic for end-to-end strategies because they imply that only one company will compete no matter how large a reward is offered. To see this, consider the following argument:

- 1) Companies will compete at the second stage *as if they had never spent a dime on R&D*. For example, suppose that the expected value of the reward is \$100 million. In that case, companies competing at the second stage can and will spend any amount up to \$100 million to win the reward. This is true regardless of what companies may have previously spent on first stage R&D.\*
- 2) Unless first stage R&D costs are zero, companies that spend \$100 million at the second stage will have a negative rate of return for the overall project.
- 3) Knowing this, companies will avoid two-stage competitions altogether. Barring accident or miscalculation, no second entrant will *ever* enter a two-stage race. This will be true no matter how large the reward is.

In order to avoid this catastrophe, efficient end-to-end proposals must establish rules that fix reward allocations so that no amount of spending at the second stage can influence payouts. This solution is very hard to reconcile with otherwise appealing schemes in which reward is tied to purchases by LDCs and/or NGOs. The reason is that companies will normally try to capture such rewards by influencing buyers through illegal kickbacks<sup>47</sup> or bundling drugs with deep discounts on other products. While criminal sanctions may go some distance toward deterring kickbacks, cross-subsidies are very hard to detect.<sup>†</sup>

Most proposals cope with the two-stage game problem by eliminating competition at the second stage. This is usually done by adopting a winner-take-all-system in which an Independent Adjudication Committee (“IAC”) awards the right to receive benefits to

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\*The general principle is, in the jargon of economics, that “sunk costs are sunk.” Suppose that a purchase commitment has an expected value of \$100 million. Suppose further that a drug company has already spent \$120 million on R&D costs. One might think that the company would stop investing in what has clearly been a losing project. However, the \$120 million is gone and cannot be recovered. For this reason, a rational company will try to improve the situation by investing up to \$100 million in additional funds.

<sup>†</sup>Companies would stop trying to influence buyers with package deals when the effective price of bundled drugs reached zero. Since LDCs do not purchase many drugs in the first place, this might or might not be an effective limit on two-stage competition.

one – and only one – company.\* This solution comes at a price, since IACs cannot use LDC/NGO purchases as evidence of how valuable drugs are to society. Furthermore, such systems give drug developers an incentive to misrepresent the potential value of their products to the IAC. These disadvantages may be less important given the market imperfections discussed in Section III.B.2. In this reading, IAC strategies reflect an implicit judgment that public health experts can determine the value of drugs at least as well as consumers.

*Hybrid Systems.* Many commentators argue that it is desirable to fund Advanced Markets and PPPs simultaneously. The most natural outcome in such a system is for PPPs to fund themselves by seeking a share of the reward. This can be done (a) directly, by delivering a winning drug before the private sector does, or (b) indirectly, by asking commercial partners to provide up-front support in exchange for patent rights if a drug is discovered. In either case, PPPs operating would be hostage to the same two-stage game problem as commercial drugmakers. We discuss these “hybrid” solutions further at Section III.C.3, *infra*.

**Other Issues.** We conclude this section by examining various other advantages and disadvantages of end-to-end strategies.

*Eliciting Information.* For reasons already described, companies competing for an end-to-end reward normally use the same mix of incentives that a pay-as-you-go sponsor would. For this reason, both strategies should be roughly comparable in their ability to elicit information. That said, drugmakers competing for end-to-end rewards may possess information that would be not available to the non-profit sector. In particular, commercial drugmakers may have superior access to (a) in-house scientists and data, (b) formal and informal networks of affiliated outside scientists, and (c) outside industrial partners. These advantages are at least partly offset by commercial drugmakers’ relative inability to exploit open source, open science, and other non-commercial methods for sharing information.

*Agency Problems (Researchers).* Like conventional patent incentives, the great advantage of end-to-end incentives is that researchers receive no payment unless a product is produced.

*Scalability.* We have emphasized that end-to-end rewards face unusually large agency problems on the sponsor side. On the other hand, these perceived risks can be mitigated if end-to-end programs are well funded and/or repeatedly pay out large sums over time. For this reason, large, well-funded programs are likely to be more cost-effective than small ones.

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\*Most proposals allow a second drug-maker to compete if it produces a substantially better product. In such systems, the first drug maker receives a reward for a period of years before being supplanted by a successor company. This solution also eliminates two-stage competition because there is no intervening period when companies are allowed to struggle for the prize.

*Political Feasibility.* The chief political advantage of end-to-end systems is that deferred payments are less visible to taxpayers.<sup>48</sup> Additionally, government officials never have to decide which scientists, scientific approaches, or scientific opportunities should be funded. This increases their ability to escape blame in the event of failure.<sup>49</sup> Finally, some politicians may find end-to-end systems inherently more congenial than alternatives that do not employ patents.

## 2. “Pay-As-You Go” Solutions.

**Description.** Pay-as-you-go solutions assume that non-profit entities can manage and outsource drug research directly, without relying on commercial drugmakers. Prior to the late 1990s, such schemes would have been little more than interesting “thought experiments.” Recently, however, the Gates, Rockefeller and other foundations have devoted substantial resources to replicating commercial portfolio management skills within non-profit PPPs. The rise of private sector “Virtual Pharmas” that outsource most of their R&D activities further suggests that outsourcing is an appealing model for drug development.

**Efficient Procurement.** The chief advantage of pay-as-you-go systems is that they offer the chance, in the American vernacular “to cut out the middleman.” Instead of specifying a reward in advance, sponsors can simply develop the drug and discover its true cost as they go along. Because the sponsor is not locked into an up-front estimate, it only pays for costs that are actually incurred. Even so, “cutting out the middleman” might not make sense if (a) in-house R&D by commercial drugmakers is significantly more cost-effective than outsourcing [Section IV.C], (b) Virtual Pharma is unable to manage drug candidate portfolios as efficiently as private drugmakers [Section IV.D, *infra*], or (c) Virtual Pharma has less ability to extract and enforce cost-effective services from outside vendors [*see, below*].

**Agency Problems (Researchers).** Sponsors may not be able to monitor and enforce outsourced work as efficiently as their commercial counterparts. This may be a function of small staffs or, alternatively, less ability to reward vendors with repeat business. Section IV.C presents evidence that these effects may be significant.

**Agency Problems (Sponsors).** Pay-as-you-go rewards are paid out (a) sooner, (b) more frequently, and (c) in smaller increments than they would be in an end-to-end proposal. These features reduce the risk that sponsors will become insolvent or otherwise renege on their obligations. Repeated payments also build a “track record” for demonstrating that sponsors are trustworthy.

**Eliciting Information.** As noted above, end-to-end and pay-as-you-go proposals should be comparably effective at eliciting information. The main difference is that pay-as-you-go proposals do not provide an incentive for drugmakers to reveal information held by in-house researchers and/or scientists participating in drugmaker research networks.

**Two-Stage Games.** Because pay-as-you-go solutions distribute rewards before drugs reach the market, they avoid two-stage game problems automatically. If duplication of R&D is desirable, sponsors can achieve similar results by using contracts, grants, or prizes to fund parallel teams.

**Scalability.** Section IV.C presents evidence that large drugmakers consistently exploit their purchasing power to extract additional value from vendors. Large, well-funded pay-as-you-go strategies should similarly be more cost-effective than small ones.

**Comment.** Assuming that the choice between pay-as-you-go and end-to-end systems depends on cost-containment, policymakers face a remarkably clear choice. On the one hand, end-to-end systems generate overpayment in proportion (on average) to uncertainties in commercial drugmakers' per-drug R&D costs. As set forth in Section IV.B, these uncertainties translate into cost penalties of 20 to 30%. Alternatively, pay-as-you-go strategies are likely to be wasteful if sponsors fail to replicate the competence, incentive structures, and/or purchasing power of commercial drugmakers. The size of these effects is an open question. If PPPs are fifteen percent less efficient than commercial drugmakers, pay-as-you-go systems will likely do a better job of cost-containment. If PPPs are forty percent less efficient, sponsors should fund end-to-end strategies instead.

### 3. Hybrid Solutions.

AdvancedMarkets proponents argue that end-to-end and pay-as-you-go solutions may be compatible. According to this scenario, sponsors would continue to fund PPPs even after an AdvancedMarkets commitment was announced.<sup>50</sup>

There is no question that AdvancedMarkets rewards would make commercial firms more willing to enter agreements with PPPs.<sup>51</sup> This, however, is not the issue. Rather, the question is whether sponsors would find hybrid systems more cost-effective than a "pure" Virtual Pharma or AdvancedMarkets strategy. There are three possible scenarios:

*AdvancedMarkets is Always Less Cost-Effective.* If AdvancedMarkets over-rewards R&D, manufacturers will compete away the profit by (a) accelerated research, (b) new collaborations with PPPs, and (c) payments to shareholders and other activities that generate no R&D. While item (b) will indeed increase the resources available to PPPs, inefficient spending on items (a) and (c) will remain. For this reason, sponsors would find it cheaper to fund PPPs directly.

*Virtual Pharma Is Always More Cost-Effective.* If AdvancedMarkets is more cost-effective than Virtual Pharma, this implies that PPPs cannot deliver research as cost-effectively as the private sector. For this reason, profit-maximizing

companies would only collaborate with PPPs if they received subsidies. Subsidizing transactions between inefficient partners is, by definition, wasteful.

*Each Institution Has Areas of Comparative Advantage.* If PPPs and private drugmakers each have significant areas of competitive advantage,<sup>\*</sup> collaboration can potentially reduce expected per-drug R&D costs. The resulting efficiency gains would manifest themselves in the form of (a) more effort elicited for any given guaranteed purchase commitment, and (b) more private resources flowing into PPPs.

Based on the foregoing discussion, hybrid strategies may make sense in some circumstances. However, there will also be a penalty to the extent that PPPs and/or AdvancedMarkets exhibit significant economies of scale. If so, sponsors may still find it more cost-effective to concentrate all of their available funds on a single strategy.

#### 4. Thinking About Cost.

Debate over the relative merits of end-to-end and pay-as-you-go systems is sometimes obscured by comparisons that fail to control for interest rates, allocation of risk, and opportunity costs. Examples include:

*Nominal vs. Discounted Rewards.* Because pay-as-you-go solutions pay out rewards sooner than end-to-end systems, the latter must be larger in nominal dollars to compensate vendors for delayed payment. In principle, funders can cover this difference by depositing the money in an interest-bearing account. More formally, the *present discounted cost* of research should be the same.<sup>52</sup>

*Risk of Failure.* A slightly more subtle issue involves the risk of failure. AdvancedMarkets proponents frequently point out that sponsors need not pay for development unless products are actually delivered.<sup>53</sup> This would not matter if each method were certain to succeed. Given that failure is possible, rational companies will insist on a larger reward to cover this risk in expectation. Once again, sponsors should be indifferent since actual payouts will (on average) be the same in either system.

*Opportunity Cost.* AdvancedMarkets proponents frequently argue that guarantees cost nothing since sponsors will eventually buy drugs anyhow.<sup>54</sup> This is only true if the commitment does not require sponsors to pay higher prices or purchase larger quantities than they otherwise would have. Given that such decisions cannot be forecast in advance, reduced flexibility will often be costly. Sponsors

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<sup>\*</sup>For example, commercial firms seldom conduct clinical trials in LDCs whereas PPPs possess extensive experience and infrastructure in this area. PPPs may also have greater knowledge of which drugs sponsors would buy if R&D succeeds.

should also consider whether alternative strategies, including pay-as-you-go research, might be even more effective.

*Near-Term Flexibility.* AdvancedMarkets proponents frequently point out that their program requires no up-front payments, allowing agencies to spend money on different resources in the near-term.<sup>55</sup> To the extent that AdvancedMarkets is paid for within existing budgets, this argument merely says that agencies can continue on existing paths until they incur the opportunity costs described above. To the extent that AdvancedMarkets is paid for by “new money,” the statement requires sponsors to increase budgets earlier than they otherwise might.

The foregoing arguments suggest that deferred payment does not, by itself, offer real economic benefits. Policymakers should instead decide between end-to-end and pay-as-you-go systems on the merits, as discussed in subparts 1 through 3, above.

“Facts are stubborn things; and whatever may be our wishes, our inclinations, or the dictates of our passions, they cannot alter the state of facts and evidence.”

-- John Adams

## IV. Evidence

We have already emphasized that there exists no single best R&D institution. Instead, policymakers must tailor R&D institutions to the particular social challenges they face. These challenges normally differ from problem to problem and also for different stages of the same problem. This section presents much of the evidence that policymakers will need to design drug development solutions. It also identifies open questions that require further inquiry.

Section A (“Available Resources”) reviews current and projected spending on neglected disease research. Although success appears to be feasible, resources are far more limited than in the private sector and the need for cost containment is correspondingly greater. Section B (“R&D Costs”) summarizes existing estimates of per-drug R&D costs. The very large uncertainty of these estimates (50 – 60%) poses a fundamental challenge to policymakers. Section C (“The Research Problem”) describes the approximately one dozen R&D steps needed to produce a drug. Our discussion focuses on identifying the dominant social challenges that must be overcome at each stage of the process. Section D (“Private Public Partnerships”) profiles current PPPs and their R&D strategies. Section E (“Do High Drug Prices Matter?”) examines the extent to which lower drug prices are likely to translate into improved health for citizens of LDCs.

### A. Available Resources

*Public and Charitable Spending.* Back-of-the-envelope estimates by Robert Ridley suggest that traditional agencies (TDR, NIH, USAID, Wellcome Trust, EU *etc.*) collectively spend about \$50 million per year on R&D for “diseases of poverty.” This figure has remained roughly constant since the 1990s and substantial future increases are unlikely. By contrast, spending by the Gates, Rockefeller and other foundations has increased markedly over the past decade. To date, most of this money has been used to create PPPs, which collectively spend about \$100 million per year on R&D. Ridley estimates that private partners have invested a comparable amount in PPP ventures, although much of this investment is in manufacturing rather than R&D *per se*. By Ridley’s estimate, the total worldwide R&D budget for neglected diseases now stands at \$250 million – a fivefold increase in the past decade. Furthermore, Ridley estimates that PPP budgets may double again by decade’s end. This would imply a worldwide R&D

effort of \$500 million per year.<sup>56</sup> This figure is still substantially smaller than the one to two billion dollars that most large drugmakers spend on R&D each year.<sup>57</sup>

Because spending is spread over roughly two-dozen entities, individual PPP budgets tend to very small by commercial standards. Typical spending goals for large PPPs – seldom realized – are about \$25 million per year.<sup>58</sup> This is only one or two percent of what large commercial drugmakers spend.<sup>59</sup>

*Rich Nation Markets.* Drug industry observers usually argue that R&D is commercially viable once annual sales reach \$250 to \$500 million.\* According to some (admittedly optimistic) estimates, selling vaccines in rich nations could provide a substantial fraction of the required revenues. Examples include malaria (\$200 million),<sup>60</sup> tuberculosis (\$113 million),<sup>61</sup> and AIDS (25% of required amount).<sup>62</sup> By contrast, rich nation vaccine markets for leishmaniasis, trypanosomiasis and other significant diseases are negligible.<sup>63</sup>

One problem with relying on Western markets is that drug R&D tends to be optimized for rich nation consumers. For example, recent commercial malaria products tend to focus on prophylactics (which are useful to visitors) rather than treatments.<sup>64</sup>

*LDC Markets.* LDC markets are almost certainly too small to support patent-driven drug discovery. Table 1 shows that developing world purchases for *all* drugs are roughly comparable to the rule-of-thumb *per drug* market sizes quoted above.† This rough-and-ready observation suggests that LDC spending for individual drugs will provide only a small fraction of what is needed.

**Table 1**  
**PhRMA Member Sales: 2002**

Geographic Area	Dollars	Share
Africa	\$549.8	0.3%
Latin America	4,583.7	2.4
Asia/Pacific (excluding Japan)	2,560.0	1.3%
India and Pakistan	483.8	0.3%
Central and Eastern Europe	\$1,390.8	0.7%
Middle East	\$1,362.3	0.7%

**Source:** PhRMA, *Profile: Pharmaceutical Industry* (2004), p. 46.

\* See Section III.B.6, below.

† The figures include drugs for rich nation illnesses like cancer and heart disease.

Estimates of potential LDC markets for individual drugs support this conclusion. For example, Prof. Kremer estimates that LDC markets could reasonably contribute about \$128 million over ten years in co-payments for a new malaria drug, \$251 million for a new tuberculosis drug, and \$442 million for a new AIDS vaccine.<sup>65</sup> These revenues should be compared to the benchmark estimated per-drug R&D cost of \$805 million.<sup>66</sup>

## B. R&D Costs.

### 1. The Accounting Cost of New Drugs

Per-drug R&D costs can be obtained directly from drug company records, estimated from the price of known inputs, and inferred from economic theory. All three methods are reviewed below.

**Direct Methods.** The first and potentially most accurate method for estimating per-drug R&D costs relies on accounting data from commercial drugmakers. This strategy requires month-by-month cost data for a large representative sample of R&D projects, including projects that are ultimately abandoned.<sup>67</sup> Over the past twenty-five years, drugmakers have successfully resisted Congressional pressure to make this information public.<sup>68</sup> In the meantime, drugmakers have made limited disclosures to researchers at the Tufts Center for the Study of Drug Development. The most recent estimate, published in 2001, is based on accounting records for 538 drug compounds first tested in humans between 1983 and 1994.<sup>69</sup> It concludes that per-drug, out-of-pocket R&D costs were \$403 million in 1997. The corresponding amortized price was \$802 million in 1997.<sup>70</sup>

Not surprisingly, drugmakers' refusal to make their accounting data available to Congress has produced massive skepticism.<sup>71</sup> Because the Tufts data are unaudited, companies could theoretically overstate their costs without fear of detection.<sup>72</sup> Nevertheless, there are several reasons to think that the data are reasonably accurate:

*Author Testimony.* Although Prof. DiMasi did not audit the drug company data, his subjective impression is that the companies were "quite straightforward and honest."<sup>73</sup>

*Aggregate Data.* Prof. DiMasi's results are broadly consistent with aggregate data reported by the industry trade group, PhRMA.<sup>74</sup>

*Other Methods.* As recounted below, other methods of estimating per-drug R&D costs are consistent with DiMasi *et al.*'s quoted errors (75% confidence).

Given that further disclosures are unlikely,<sup>75</sup> DiMasi's estimates will likely to remain "state-of-the-art" for the foreseeable future.

**Estimates Based on Known Input Prices.** Practically all R&D services are available on the open market. In principle, per-drug R&D costs can be estimated by preparing a *pro forma* budget based on (a) the market price of each required R&D step, and (b) adjustments for the cost of failed projects and interest rates. To date, the best-known example of this approach is due to the Global Alliance for TB Drug Development.

*Required Research Tasks.* Global Alliance estimates that Phase I through III tests will cost \$26.6 million for each potential tuberculosis drug tested.<sup>76</sup> Process development (chemistry, manufacturing, and controls) adds another \$5.3 million for a total of \$31.9 million.<sup>77</sup> This is just twenty-six percent of the \$125 million figure quoted by DiMasi *et al.*<sup>78\*</sup>

*Adjusted Total.* After including imputed interest expenses and the cost of failed drug candidates, Global Alliance puts the final cost of clinical trials at between \$76 and \$115 million.<sup>79</sup> It then makes a very rough estimate that discovery phase costs would add another \$40 to \$125 million.<sup>80</sup> This yields a total per-drug R&D cost of between \$115 and \$240 million.<sup>81</sup> This is only seventeen to twenty-six percent of the \$684 to \$936 million (95% confidence limit) range quoted by DiMasi *et al.*<sup>82</sup>

*Analysis.* The DiMasi *et al.* results are average figures and hide enormous variability from test-to-test.<sup>†</sup> For this reason, they are not necessarily inconsistent with Global Alliance's estimate. Alternatively, the Global Alliance figures could suffer from methodological problems. The input costs that PPPs use to compile budget estimates are known to show "enormous variability" and these differences are poorly understood. Knowledgeable commentators argue that they should be approached with "great caution."<sup>83</sup>

If we assume instead that the discrepancy between the DiMasi and Global Alliance estimates is real, the most likely explanation is that DiMasi's figures include additional drugmaker spending on redundant and/or accelerated development compared to a simple bare-bones R&D program. [Section III.B.5 *infra*].

**Estimates From Revenues.** Prof. Kremer argues that the "most attractive approach" to estimating per drug R&D costs is from drugmaker revenues. Starting with reported revenues, he estimates that drugs that appeared on the market in 2000 earned profits equal to a present discounted value of \$525.2 million. As noted in Section III.B.3, we expect revenues in a competitive market to equal drugmakers' combined R&D and marketing costs. Based on published reports that marketing comprises about 15% of all variable costs, Kremer arrives at an estimated per drug R&D cost of between \$2.5 and \$5.0 billion. He selects \$3.0 billion as the number most likely to apply to neglected disease R&D. This number, Kremer assumes, is larger than the low development cost

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\* Unlike DiMasi *et al.*, Global Alliance also estimates pre-clinical costs explicitly. It puts these at between \$4.9 and \$5.3 million. Global Alliance, *Economics of TB Drug Development*, *supra* at p. 37.

† More formally, DiMasi *et al.* quote standard deviations for Phase I through III trials ranging from 70% to 94% of the corresponding mean values.

associated with some technologically easy drugs yet stops short of the very large revenues earned by “blockbuster” products.”<sup>84</sup>

The basic problem with this approach is that it replaces one uncertainty (R&D costs) with another (marketing expense). Some idea of these difficulties is evident from Berndt *et al.*'s recent attempt to refine Prof. Kremer's estimate. They start by noting that published estimates place marketing costs at between 15 to 36%, but then criticize these figures and adopt a lower, ten percent estimate instead. Plugging this estimate into their calculation pushes the required reward up to \$2.56 billion. They then adjust their result a second time (to \$3 billion) based on the claim that “a malaria vaccine may be more difficult to develop than the typical new chemical entity.”<sup>85</sup>

Finally, even if the marketing figure were known, Prof. Kremer's argument might still overstate drugmaker R&D costs. Since drugmakers would not knowingly operate at a loss, revenues do indeed provide a convincing upper bound on expected per-drug R&D costs. However, R&D costs will only be *equal* to the figure if markets are competitive. This assumption may not be realistic if (a) drugmakers are able to collude, or (b) R&D costs are a significant fraction of the expected market so that only a limited number of entrants can enter the market. In this case, per-drug R&D costs could be significantly lower than. Kremer's argument suggests.

**Comment.** All of the foregoing methods measure the *accounting* cost of developing new drugs. However, sponsors are actually interested in the minimum feasible cost. Section III.B.2 has already explained why this figure could be significantly lower than the accounting cost. We return to this point in Section 5, below.

## 2. Predicting Future Costs.

Cost estimates are historical. However, policy planners must set incentives up to fifteen years into the future. One obvious procedure is to use the observed growth of per-drug R&D costs to extrapolate future costs from current estimates. This procedure faces several problems:

*Rates Are Poorly Known.* Growth rates are derived by comparing per-drug R&D costs from different decades. However, we have already emphasized that these estimates are highly uncertain. These uncertainties automatically infect growth rate estimates.<sup>86</sup>

*Rates Are Quoted for the Recent Past.* Because studies are historical, they usually report per-drug R&D costs that are approximately five years old. Furthermore, the studies themselves only appear at ten-year intervals. For this reason, policymakers' knowledge of current R&D costs can be up to fifteen years out of date. At some point, policymakers may decide that it is better to discard DiMasi *et al.*'s estimates in favor of methods based on input prices and/or sales revenues.

*Rates Change By Large Amounts.* DiMasi reports that total R&D costs rose at a real annual rate of 7.0% in the 1970s and 7.6% in the 1980s.<sup>87</sup> However, this apparent stability is misleading. During this same interval, real annual growth rates for the “clinical” component of testing rose from 6.1% real annual rate to 11.8% while rates for pre-clinical testing fell from 7.8% to 2.3%.<sup>88</sup> If similar shifts occurred today, growth rate estimates could easily be off by a factor of two.

*Shocks are Likely.* The foregoing data suggest that growth rates change dramatically on time scales that are similar to the twelve-year life of most R&D projects.<sup>89</sup> While many drugmakers believe that growth rates will decline over the next decade, this prediction is highly uncertain. Similar forecasts made ten years ago were dramatically wrong.<sup>90</sup>

The foregoing discussion suggests that sponsors’ ability to estimate the rate at which R&D costs are growing may be uncertain to within a factor of two. This additional uncertainty makes the problem of choosing the reward even harder. Suppose, for example, that sponsors believe that costs are growing by ten percent whereas actual increases are only five percent. According to this pessimistic-but-plausible scenario, the estimated reward would be forty percent larger than it needs to be.

### 3. Refinements.

DiMasi reports that testing costs vary dramatically from drug to drug. Furthermore, this variability continues to grow as drugs proceed through the later – and more expensive – phases of drug discovery.<sup>91</sup> Improved methodologies can reduce these uncertainties at the margin, but fundamental improvements are unlikely.<sup>92</sup>

A more promising approach is to recognize that DiMasi *et al.*’s estimate represents an average over many dissimilar R&D projects. In theory, policymakers may be able to improve their estimates by taking account of project-specific factors. These include:

*Disease Type.* R&D tends to be especially costly for (a) chronic and degenerative diseases, which may take years to show up in testing,<sup>93</sup> (b) diseases that cannot be reproduced in mice or other animal models,<sup>94</sup> (c) compounds that lack analogs to known drugs, (d) diseases for which underlying biological knowledge is limited,<sup>95</sup> or (e) drugs that must be tested in multiple target populations.<sup>96</sup> However, it is unclear how accurately sponsors can adjust estimates to take account of these factors. This is particularly true for neglected diseases, where lack of experience since the 1960s makes pre-human test costs highly uncertain.<sup>97</sup>

*Ambitious Goals.* R&D costs vary depending on the level of difficulty of synthesis or extraction, as well as desired drug characteristics.<sup>98</sup> Several PPPs are currently pursuing R&D projects that have no existing precedent.<sup>99</sup>

*Low-Hanging Fruit.* Researchers have already found many of the easiest cures and treatments for rich nation diseases.<sup>100</sup> By contrast, basic research for neglected diseases remains crude.<sup>101</sup> Additionally, commercial firms have produced a backlog of promising drugs that (a) were abandoned in testing for non-scientific reasons, or (b) could be readily adapted to treat new populations and/or diseases.<sup>102</sup> This backlog is substantial but could also be exhausted within a few years' time.<sup>103</sup>

*Drugs vs. Vaccines.* Compared to drugs, vaccines tend to be technically complex, require longer clinical trials, and are more expensive to produce.<sup>104</sup>

*Lower Costs in LDCs.* Global Alliance argues that holding trials in LDCs would cut clinical testing costs by sixty percent. The reasons are said to be lower labor costs and – for vaccines – high infectivity rates that permit researchers to extract statistically significant results from smaller populations.<sup>105</sup> These savings are at least partly offset by higher infrastructure and political expenses.<sup>106</sup> Anecdotal evidence suggests that per-patient Phase III costs in Thailand are similar to those found in rich nations.<sup>107</sup>

*Technology.* Some companies claim that advanced technology can substantially reduce R&D costs. The effect is limited by the fact that savings tend to be largest for pre-human R&D,<sup>108</sup> which is comparatively inexpensive in any case. Nevertheless, some companies claim that technology can cut costs for human trials as well.<sup>109</sup>

It is currently unclear whether and to what extent sponsors can reduce DiMasi *et al.*'s quoted uncertainties by making adjustments for individual projects. However, Global Alliance's quoted uncertainty of thirty-four percent for a new tuberculosis drug suggests that current state-of-the-art offers relatively little room for improvement. This may change over the next decade as PPPs gain more first-hand experience managing drug portfolios.

#### 4. Average vs. Marginal Accounting Costs.

Drugmakers respond to incentives differently, with low-cost firms entering the market sooner than other entities. This suggests that sponsors should tailor to low-cost firms instead of an industry-wide average.<sup>110</sup> The problem, in practice, is that companies try to keep any cost advantage secret. Trade press accounts provide only approximate clues to how much sponsors can trim rewards before even the lowest cost companies drop out of the market.<sup>111</sup>

Sponsors who expect companies to earn at least part of their return from commercial sales face a second difficulty. Anecdotal evidence suggests that companies have widely different opinions about the profitability of neglected disease research<sup>112</sup> and that small biotech firms are generally more optimistic than large drugmakers.<sup>113</sup> In

principle, sponsors should offer lower subsidies when companies are optimistic. In practice, companies will try to hide their optimism.

## 5. Do Accounting Data Overstate The Minimum Feasible Cost?

So far, we have concentrated on what commercial drugmakers actually spend to develop new drugs. What sponsors would actually like to know, however, is the *minimum* cost of developing the drug. Even if drugmakers' accounting records were completely known, they would say very little about this figure.

As explained in Section III.B.2, we expect the total R&D budgets of firms in a discovery race to equal the patent reward. Except for the special case where the cost of pioneer and “me-too” drugs are exactly the same, competitive pressures will normally encourage drugmakers to fund accelerated and/or duplicative R&D projects that inflate accounting costs. This effect appears to be substantial. For example, DiMasi *et al.* report that drug companies spend 35% more for drugs that are eventually approved than for drugs that are ultimately abandoned.<sup>114\*</sup> They speculate that this result reflects competitive pressures to accelerate discovery by performing studies concurrently instead of seriatim.<sup>115</sup> Similarly, they find that R&D costs are 36% higher when drugmakers pay FDA to give their drugs “priority” status. They argue that the effect is at least partly based on a judgment that such drugs are “commercially significant.”<sup>116</sup>

## 6. Estimated Uncertainty and Expected Overpayments.

The foregoing sections suggest that estimated per-drug R&D costs are highly uncertain. Various lines of evidence can be used to quantify this uncertainty:

*Prof. Kremer.* Prof. Kremer estimates that the annual sales required to elicit investment in new drug development lies between \$250 - \$500 million.<sup>117</sup> The high estimate is twice the low estimate.

*AdvancedMarkets.* The AdvancedMarkets study group estimates that the per-dose guaranteed price required to elicit R&D lies between \$15 and \$25. The high estimate is 140% of the low estimate.

*DiMasi et al. (95% confidence).* DiMasi *et al.* estimate with 95% confidence that per-drug R&D costs lie between \$684 and \$936 million.<sup>118</sup> The high estimate is 127% of the low estimate and includes a five percent chance that the true number falls outside the quoted window.

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\*Costs for Phase II trials were 77% higher for drugs that were eventually approved than for drugs that successfully completed Phase II before being abandoned. Similarly, Phase III costs were 18% higher for drugs that eventually received FDA approval. Joseph DiMasi, Ronald Hansen & Henry Grabowski, “The Price of Innovation: New Estimates of Drug Development Costs,” *Journal of Health Economics* 22:151 (2003) at pp. 171-72.

DiMasi *et al.* (75% confidence). DiMasi *et al.* quote a range of \$757 million to \$854 million with 75% confidence. The high estimate is 111% of the low estimate and includes a twenty-five percent chance that the true number falls outside the quoted window.

*Global Alliance.* Global Alliance estimates that developing a new tuberculosis drug would have a capitalized cost of between \$115 and \$240 million.<sup>119</sup> The high estimate is 152% of the low estimate.

*PPP Budget Estimates.* Estimates of how much PPPs will need to spend to support existing programs through 2007 vary between \$1.2 and 2.2 billion.<sup>120</sup> The high estimate is 146% of the low estimate.

*Other Published Estimates.* Many authors have estimated the market size required to elicit commercial R&D. Typical values range between \$200 and \$500 million.<sup>121</sup> The high estimate is 160% of the low estimate. Similarly, Nwaka and Ridley report that published estimates of per-drug R&D costs are “in the range of US \$0.5 – 1 billion.”<sup>122</sup> The high estimate is 150% of the low estimate.

As explained in Section III.B, many R&D proposals (*e.g.*, AdvancedMarkets) require sponsors to promise specific rewards in advance. The uncertainties quoted above provide information about how much these institutions are likely to overpay on average. Sponsors face the following choices:

*Low Risk, High Cost Strategy.* The sponsor can elicit R&D investment with 100% certainty by announcing a reward equal to the highest cost estimate. It will then overpay by, on average, half the cost range.\* For the case of a fifty percent range, the average overpayment will be 25%. This overpayment is in *addition* to any overpayments that drugmakers themselves expect to make when purchasing R&D from in-house employees or outside vendors. Based on the foregoing discussion, AdvancedMarkets-type proposals can expect to overpay by twenty to thirty percent.<sup>†</sup>

*Medium Risk, Lower Cost.* Sponsors who choose rewards within the quoted cost range can reduce the expected overpayment. By doing so, however, they increase the risk that the promised reward will fail to elicit investment.

High average expected overpayments constitute the main objection to AdvancedMarkets and other end-to-end proposals. Virtual Pharma solutions avoid this difficulty by paying for R&D costs as they arise. We shall see, however, that Virtual Pharma and other pay-as-you-go solutions are likely to overpay for other reasons.

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\* This is true whenever probable costs are distributed symmetrically around the range’s mid-point. Where this condition is violated, average expected costs may be higher or lower, although they will never exceed the range itself. Given the state of existing R&D cost uncertainties, such refined models are not justified.

† The uncertainties quoted by DiMasi *et al.* are significantly smaller than the other sources cited above. This may be because the DiMasi study focuses on just one component – R&D costs – that goes into drug companies’ overall decision to invest.

Policymakers should evaluate these drawbacks against the twenty to thirty percent overpayment expected for AdvancedMarkets.

## C. The Research Problem

This section reviews the roughly one dozen separate and distinct R&D steps that comprise the drug development pipeline. While each step poses its own individual challenges, a few generalizations are possible:

*Cost.* R&D becomes steadily more expensive as drugs progress through each successive stage of the pipeline. Three-quarters of all expenditures occur after drugs enter the preclinical stage.<sup>123</sup> Seventy percent of all R&D is spent after clinical testing begins.<sup>124</sup>

*Information.* The need to collect widely scattered ideas and information declines steadily as drugs progress through the pipeline. New drug candidates are frequently compounds that have never been synthesized – let alone investigated – before. Because researchers are forced to break new ground, accessing existing stores of human knowledge is less important.

*Agency Problems.* Sponsors find it hard to monitor and control early-stage R&D, which requires researchers to exercise substantial discretion and creativity. At least by comparison, late-stage human trials tend to be fairly routinized and mechanical.

Since the 1980s, drugmakers have increasingly outsourced all phases of drug R&D. Today, large drug companies spend about thirty percent of their R&D budgets on outside collaborations<sup>125</sup> and an additional 10% on drugs “licensed in” from other companies.<sup>126</sup> Consultants predict that companies will continue to purchase more and more research through outsourcing, licenses, mergers, and other similar transactions.<sup>127</sup> The most extreme expression of this strategy is the emergence of “Virtual Pharmas” that outsource all R&D functions except for portfolio management, study design, and interactions with regulators.<sup>128</sup> For the moment, it is still not clear whether Virtual Pharmas can be as cost-effective as traditional in-house drugmakers. Nevertheless, investors’ willingness to fund Virtual Pharma companies represents a market judgment that outsourced R&D is at least approximately competitive with traditional in-house development.<sup>129</sup>

The great advantage of outsourcing is that it lets companies cut costs by delegating work to low cost vendors and/or purchasing access the latest technologies.<sup>130</sup> However, outsourcing can also increase costs if companies are not able to monitor the value and cost of vendors’ work. The fact that large drugmakers fund almost all of their R&D investments from internal cash flows suggests that investors find it hard to monitor company research and therefore demand a premium to cover the risk of being misled.<sup>131</sup> On the other hand, the fact that venture capital firms routinely invest in biotech

companies suggest that these risks are manageable.<sup>132</sup> PPPs are acutely aware of these agency problems.<sup>133</sup>

Non-commercial drug development is rare but not unprecedented. Historically, government agencies have sometimes taken the lead in developing new vaccines, finding drugs for biological and chemical weapons defense, and even combating malaria.<sup>134</sup> More commonly, government agencies and NGOs have extensive experience in identifying and funding outside projects,<sup>135</sup> providing drug screening and other support services for industry, and building infrastructure for clinical trials.<sup>136</sup>

The remainder of this section provides a step-by-step description of the drug discovery pipeline. We focus on social obstacles throughout.

## 1. Basic Research.

Effective R&D requires detailed knowledge of disease organisms and how they interact with the human body. Governments and charities pay academic, non-profit, and commercial institutions to perform this work.<sup>137</sup> Compared to rich nation diseases, the basic knowledge available to support neglected disease research is very weak. Depending on the disease, filling this gap could take two to twelve years.<sup>138</sup>

**Agency Problems.** Funding agencies seldom have sufficient knowledge and expertise to judge research proposals for themselves. For this reason, they usually rely on peer review.

**Eliciting Information.** In the long run, academic publish-or-perish incentives encourage researchers to transmit their results to others. However, competition for publishing priority often discourages information sharing in the short run. Academic patenting creates further incentives to hoard information, although the effect seems to be small.<sup>139</sup>

Commercial R&D tends to be much more restricted. For example, private sector firms currently generate about sixty percent of the world's genomics data. Much of this data is held within individual companies, with the most valuable data appearing in patent applications after several years.<sup>140</sup> Other data is also sold commercially through subscription services and off-the-shelf tools.<sup>141</sup> In many cases, data are priced beyond the means of typical academic and non-profit scientists. The problem is mitigated by the fact that commercial companies possess relatively little neglected disease data in any case.

**Efficient Procurement.** In practice, most basic research is funded by grants. As explained in Section III.C.5, grant researchers face relatively little pressure to contain costs beyond an implicit promise that the value of their work will exceed the grant agency's investment. At the same time, the danger of overpayment is relatively unimportant since basic research represents only a small fraction of total R&D expenditures.

*Patent Issues.* Many grant bodies permit and even require researchers to patent their discoveries. The existence of patents can have a profound effect on the price that sponsors pay for R&D and manufacturing throughout the drug’s lifecycle.

**Principal Social Challenges.** Basic research requires large amounts of creativity and discretion. For this reason, sponsors find it relatively hard to monitor and control researchers. Scientific progress may also require researchers to share and combine widely scattered information. Practically all commentators agree that grants provide a more efficient mechanism than patents at this stage.<sup>142</sup>

## 2. From Idea to Target Validation.<sup>143</sup>

<b>Cost</b>		
Out-of-Pocket		<Moderate>
<b>Time</b>		
To Next Stage		1-2 years
<b>Risk</b>		
Transition to Next Stage		30-50%

Basic understanding of how diseases work yields ideas for manipulating and interfering with them. Researchers use these ideas to find proteins (“targets”) that control metabolic functions within the human body. Drug companies currently use about 500 targets to make drugs, although thousands exist.<sup>144</sup> Once targets have been identified, chemistry and biology experiments can be used to determine which proteins show the most promise.

The fact that multiple ideas lead to “hits” on the same protein may also be significant. Typically, about ten proteins survive this winnowing process to become “validated targets.” However, the actual number of targets can vary widely from disease to disease.<sup>145</sup>

**Eliciting Information.** Two-thirds of all new drug ideas are generated by government- and university-supported research.<sup>146</sup> Commercial drugmakers learn about these ideas by (a) monitoring the scientific literature, (b) maintaining informal contacts throughout the scientific community, (c) paying academic scientists to act as consultants and sit on advisory boards, and (d) purchasing compounds developed by academic start-up companies.<sup>147</sup> Anecdotal evidence suggests that these mechanisms work poorly for neglected diseases. Commentators complain that much basic research is not practical and that there are not enough institutions for channeling good ideas into non-profit development pipelines.<sup>148</sup> These effects may be partly offset by government agencies, which provide limited funding support for the discovery and development of promising ideas.<sup>149</sup>

Commercial research is less often shared. Commentators complain that companies pursuing neglected disease research often pursue separate – and inefficiently small – projects instead of pooling information.<sup>150</sup> Confidentiality is particularly important for information that cannot be patented, including notably including experimental data which show that seemingly promising targets are actually “dry holes.”<sup>151</sup>

*Patent Issues.* The small number of potential protein targets implies that it would be relatively easy for researchers to find and patent all of them. While such patents have historically been worth little, growing sponsor budgets could change that within a few years. We argue in Section V.C.4 that commercial patents on early stage research are likely to increase sponsor costs for most plausible development strategies. In principle, sponsors can protect the public domain by paying academic researchers to find and publish targets so that nobody can patent them.\*

The small number of possible targets also implies that neglected diseases may sometimes be treatable by drugs that were originally developed for other applications. These are overwhelmingly drugs for rich nation diseases. In some cases, patents for these drugs may already have expired, increasing the public domain. In others, sponsors must negotiate licenses and pay patent owners a premium for access to their knowledge.

**Agency Problems.** The fact that biotech companies usually sell ideas to large drugmakers *after* they have been turned into specific compounds suggests that drugmakers find it hard to evaluate the promise of early-stage innovation.<sup>152</sup> In the commercial sector, drugmakers frequently solve these problems by purchasing “external innovation” from biotech companies.<sup>153</sup> These transactions, which typically feature large rewards, closely resemble a prize system.

**Efficient Procurement.** Grant supported research does a poor job of cost containment. However, even large overpayments in percentage terms will normally have a relatively insignificant impact on total R&D budgets. If ideas and targets are patented, owners may insist on a significant premium for their work.

**Principal Social Challenges.** Target identification and optimization face strong agency problems on the researcher side. Furthermore, firms invest extensive effort in eliciting promising ideas. The non-profit sector has yet to develop analogous institutions for channeling ideas into neglected disease research.

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\* Large drugmakers followed this strategy a decade ago when they paid a group of academic scientists known as The SNP Consortium to find and publish single nucleotide polymorphisms so that small biotech firms could not patent them.

### 3. Lead Compound Identification<sup>154</sup>

<b>Cost</b>		
Out-of-Pocket		\$100,000 – \$1 million
<b>Time</b>		
To Next Stage		~ 1 Year
<b>Risk</b>		
Transition to Next Stage		60 - 65%

Designing drugs is astronomically harder than finding a needle in a haystack. In principle, there are roughly  $10^{40}$  “small molecules” that might be used as drugs. Only a handful of these are actually useful.<sup>155</sup> Drugmakers start by identifying “lead compounds” that have desirable effects on target proteins. Although these compounds are not suitable as drugs, laboratory chemists can use them as a starting point for developing feasible drugs.

There are currently four broad strategies for finding “lead compounds”:

*High Throughput Chemistry.* Large drugmakers hire staff chemists to create “libraries” containing tens of thousands of chemicals. They then use robots to screen the libraries against promising targets. Automated screening reportedly costs a few dollars per sample or about \$1 million per search.<sup>156</sup> Because the libraries sample a minuscule fraction of the  $10^{40}$  possible drug molecules, the quality of individual libraries depends on size. Competing libraries have negligible overlap.\*

*Combinatorial Chemistry.* Combinatorial chemistry experiments blend a handful of building block molecules to create hundreds of thousands or millions of compounds at once. Lead compounds are identified if and when one of these compounds binds to the target protein. Substantial combinatorial chemistry capabilities exist in both universities and industry. Individual experiments typically costs tens of thousands of dollars. In principle, combinatorial chemistry permits researchers to screen many more compounds than exist in any library. Unlike traditional libraries, however, the chemicals generated by combinatorial chemistry experiments are non-random and are often biased toward molecules that are not likely to produce useful drugs. Drug companies have devoted enormous resources to solving the problem and claim to see early evidence of improvement.<sup>157</sup>

*Computational Biology.* Current-generation computers have a useful, but highly imperfect ability to predict chemical reactions between molecules. In principle, computer simulations permit scientists to simulate the behavior of compounds that have never been synthesized. For now, the best simulation programs are built and maintained by university scientists. Building a capability typically costs more than \$250,000. Once established, however, the marginal cost for performing

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\* Most the overlap that does exist involves standard chemicals purchased from commercial suppliers.

individual searches is relatively small.<sup>158</sup> The motivation and creativity of individual researcher has a modest influence on success or failure.

*Short Cuts.* In some cases, lead compounds may already be known from anecdotes, folklore, serendipitous research, or prior R&D. Prominent short cuts include (a) using natural substances found in the body as analogs for synthetic drugs,<sup>159</sup> (b) “bioprospecting” for traditional medicines in Africa, China, and Southeast Asia,<sup>160</sup> (c) developing products that have been previously abandoned,<sup>161</sup> or (d) using drugs that are already known to target the same protein in the context of other diseases.<sup>162</sup>

For well-funded rich nation diseases, worldwide screening programs typically produce perhaps ten lead compounds for each known protein target. Each of these compounds can, in theory, be used to develop a separate family of drugs.<sup>163</sup>

**Eliciting Information.** Knowledge of possible “short-cuts” is widely scattered across the globe; eliciting this information poses a formidable social challenge. Nwaka and Ridley stress that scientists in LDCs possess an inherent information advantage in deriving leads from natural products and traditional medicines.<sup>164</sup>

Absent such shortcuts, researchers have little or no *a priori* of whether a particular compound library, combinatorial chemistry experiment, or computational biology simulation will produce suitable candidates. In this case, social institutions are no help: The only way to find out is to do the experiment.

**Agency Problems.** High throughput chemistry has minimal agency problems. First, it is a largely robotic process that can be easily monitored by sponsors. Second, researchers also have little or no *a priori* knowledge of whether they will find leads. The risks are scientific, not social.

Because combinatorial chemistry experiments are individually designed, they depend on the motivation and judgment of individual researchers. Computational biology similarly demands significant, if somewhat less, discretion and creativity from researchers. For this reason, both methods pose significant agency problems.

Once a lead compound has been discovered, sponsors can confirm its properties by independent experiment. To this extent, agency problems are minimal. Researchers may, however, possess specialized knowledge about whether particular compounds can be turned into drugs and/or whether consumers would value such drugs if they existed (*see, infra*). The fact that drugmakers sometimes purchase R&D rights at the lead compound stage suggests these agency problems are manageable and can be further reduced by designing contract provisions (*e.g.* milestone payments) that require researchers to share future development risks.<sup>165</sup>

**Efficient Procurement.** Private funds are usually available to screen targets for rich nation diseases. In this case, subsequent development takes place within the patent

system. The emergence of non-proprietary chemical libraries<sup>166</sup> also makes it possible to purchase high-throughput screening services outside the patent system.

Commercial screening is rarely available for neglected diseases. Historically, a few government agencies have provided in-house services to help close this gap.<sup>167</sup> More recently, some PPPs have persuaded drugmakers to donate access to compound libraries. Both options cost sponsors little or nothing. In principle, sponsors can also purchase screening services under contract. Assuming competent bargaining and/or competitive bidding, cost containment should be efficient. Since screening services are relatively inexpensive, even large overpayments are likely to have only a minimal impact on total R&D costs.

**Principal Social Challenges.** High throughput screening is expensive but entails minimal social challenges. Other methods of finding lead compounds are less expensive but suffer from substantial agency and information problems.

#### 4. Lead Compound Optimization<sup>168</sup>

<b>Cost</b>		
Out-of-Pocket		Millions to Tens of Millions
<b>Time</b>		
To Next Stage		1+ Years (%)
<b>Risk</b>		
Transition to Next Stage		55%

Once a lead compound has been discovered, chemists modify it to find potentially workable drugs. Drugmakers must then decide whether the new compounds are sufficiently promising to warrant testing. Neglected disease research has relatively few institutions for optimizing drugs.<sup>169</sup> Although government agencies have tried to fill this gap, commentators claim that they are often unsuccessful.<sup>170</sup>

**Eliciting Information.** The number of possible small molecules is so large that drugmakers are usually the first human beings ever to synthesize and test these chemicals. However, sponsors may

be able to elicit valuable ideas about how lead compounds might be modified and, especially, which compounds are likely to succeed.

**Agency Problems.** Drug optimization potentially involves at least three groups of researchers. Each group presents potential agency problems:

*Chemists.* Chemistry is creative and hard to monitor. Nevertheless, the fact that large drugmakers routinely outsource work to contract research companies<sup>171</sup> suggests that these risks are manageable. The agency problems associated with chemistry outsourcing are further discussed at Section III.C.6, *infra*.

*Commercial Drugmakers.* Once chemicals have been synthesized, they must still be evaluated. Drugmakers claim to possess superior experience<sup>172</sup> and research tools<sup>173</sup> for identifying and rejecting molecules that are likely to fail in testing.

They also have superior knowledge of whether a successful drug is likely to be profitable.<sup>174</sup> The fact that biotech companies usually sell R&D results after lead optimization<sup>175</sup> suggests that these agency problems are manageable. Risks can also be shared by structuring deals that include milestone payments based on success in subsequent trials.<sup>176</sup>

PPPs have devoted extensive resources to replicating drugmakers' specialized scientific knowledge of when drugs are likely to succeed. This includes hiring former executives and obtaining advice from present-day employees. Drugmakers' specialized commercial knowledge is largely irrelevant for neglected diseases, where procurement decisions are usually made by small groups of sponsors.<sup>177</sup>

*Academic Biologists.* Some commentators argue that academic scientists are unlikely to perform routine screening efficiently because they see it as repetitive and un-prestigious.<sup>178</sup> Others claim that academic scientists would be enthusiastic participants if funding agencies spent more money on proof of concept and project management activities.<sup>179</sup>

**Efficient Procurement.** Research chemistry and biology testing services can be purchased under contract. As noted in Section III.C. 6, these services are competitively supplied. It is therefore reasonable to think that PPPs can obtain services at or near vendors' cost.

**Principal Social Challenges.** Sponsors face modest agency problems in synthesizing and evaluating candidate drugs. PPPs claim to have acquired much of this specialized knowledge by hiring former industry executives.

## 5. Pre-Clinical Testing.<sup>180</sup>

<b>Cost</b>		
Out-of-Pocket		\$2.5m - 5.0m
<b>Time</b>		
To Next Stage		3 to 6 months
<b>Risk</b>		
Transition to Next Stage		50 – 60%

Preclinical trials use tests on tissue cultures and animals to determine the risk that a compound poses to man and the environment. They also document how effectiveness and/or toxicity vary with dose. Although preclinical trials are usually performed before human testing, long-term studies are sometimes deferred until therapeutic potential has been demonstrated in patients.<sup>181</sup> One-third (31.4%) of all new drugs also include a long-term animal testing program.<sup>182</sup>

Government agencies often fund pre-clinical programs.<sup>183</sup> Some government and/or government-funded laboratories possess specialized equipment and expertise not found in the private sector.<sup>184</sup>

**Efficient Procurement.** Drugmakers routinely contract pre-clinical testing out to commercial laboratories. The large number of contract vendors suggests that prices are competitive.<sup>185</sup>

**Agency Problems.** Drugmakers possess specialized knowledge about scientific opportunities, FDA regulatory environment, and commercial potential. (*See below*). This information sometimes permits them to design pre-clinical trials that weed out drug candidates early, avoiding the expense of human trials.<sup>186</sup>

Contract researchers follow well-defined protocols, have relatively little discretion, and generate standardized data. This work is relatively easy to supervise as long as researchers remain reasonably honest. However, it is sometimes harder for sponsors to detect instances of outright fraud. Anecdotal evidence suggests that contract researchers sometimes fabricate data to avoid work,<sup>187</sup> prolong unproductive (but lucrative) research, or to please sponsors.<sup>188</sup>

The foregoing problems are presumably manageable, since drugmakers routinely purchase promising preclinical drugs from biotech companies<sup>189</sup> Up-front fees average \$2 million with an additional \$15 million in milestone payments.<sup>190</sup>

**Eliciting Information.** Researchers performing pre-clinical tests are often the first human beings ever to evaluate these chemicals. In such cases, the value of outside information is probably minimal. Outside information may be more important when researchers try to develop drugs from existing medicines.

**Principal Social Challenges.** Agency problems exist but appear to be manageable.

## 6. Process Development.<sup>191</sup>

<b>Cost</b>		
Out-of-Pocket		\$50m
<b>Time</b>		
To Next Stage		Up to 4 Years for Vaccines
<b>Risk</b>		
Transition to Next Stage		<?>

Chemical engineers must turn laboratory scale, experimental compounds into working drugs. Following the start of clinical trials, companies may change the initial formulation several times<sup>192</sup> to achieve a variety of goals:

*Stability.* Active ingredients must be stabilized against temperature, humidity, light, and bacterial growth.<sup>193</sup>

*Bioavailability.* Formulations must allow active ingredients to enter the bloodstream in a suitable form and strength.<sup>194</sup>

*Scalability.* Laboratory and pilot-scale manufacturing methods must be scaleable to full-scale manufacturing.<sup>195</sup> Process engineers must also find bulk raw materials suppliers and transfer technology to a full-scale manufacturing site.<sup>196</sup> These tasks must be performed earlier for vaccines, which cannot be modified after testing.<sup>197</sup>

*Reproducibility.* Methods must be reasonably replicable within and between batches. These requirements usually become more stringent following Phase I trials.<sup>198</sup> Analytical methods (“assays”) must be developed to detect impurities and degradation products at the 0.1% level.

*Economical.* Contract suppliers must typically slash API prices from \$5,000 per kilogram in Phase I to 1,000 per kilogram in Phase III and \$500 per kilogram in full-scale production.<sup>199</sup> This usually means inventing new processes that include fewer manufacturing steps.<sup>200</sup> Chemical engineers’ ability to meet these requirements introduces “a large element of uncertainty”<sup>201</sup> into the overall R&D process. In some cases, process design is further constrained by the need to avoid existing patents.<sup>202</sup>

*Safety.* Chemical companies must modify Phase I processes to devise safer processes for use in Phase II and III production.<sup>203</sup> Research may fail if it is impossible to manufacture the drug safely.<sup>204</sup>

*Regulatory Compliance.* Engineers must create and obtain regulatory approval for Current Good Manufacturing Practices (cGMP) documentation for the foregoing.<sup>205</sup>

Process engineering is one of two R&D phases where outsourcing reportedly yields significant savings over in-house development.\* Commentators claim that outsourcing cuts process development costs by about five percent.<sup>206</sup>

**Eliciting Information.** Companies frequently outsource process development because outside vendors (a) possess essential expertise in synthesizing complex compounds, or (b) can do the job at lower cost.<sup>207</sup> In addition to corporate vendors, individual scientists often have important information and ideas to contribute. Experts are scattered around the world, including Eastern Europe and the former Soviet Union.<sup>208</sup> Manufacturers frequently use prizes to obtain ideas for solving particularly recalcitrant problems.<sup>209</sup>

**Efficient Procurement.** Contract chemical companies offer a complete range of process development services for small molecules<sup>210</sup> and biopharmaceuticals.<sup>211</sup> Individual vendors often form alliances that can handle all phases of process development from pre-clinical gram-scale synthesis through full-scale production.<sup>212</sup>

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\* The other phase is manufacturing.

More than 1200 companies provide custom development services worldwide.<sup>213</sup> Companies compete fiercely on price,<sup>214</sup> quality, respect for intellectual property, customer service, regulatory issues, R&D capabilities,<sup>215</sup> and FDA track records.<sup>216</sup> Customers use a variety of tactics to exploit and promote this competition:

*Competitive Bidding.* Drugmakers frequently employ competitive bidding to contain prices.<sup>217</sup> New projects typically receive ten or more bids.<sup>218</sup>

*Monitoring.* Companies create in-house outsourcing teams and insist that vendors hire specific liaisons for the teams to deal with.<sup>219</sup>

*“Preferred Supplier” Status.* Many companies are moving away from short-term, lowest cost suppliers to long-term custom manufacturing partners.<sup>220</sup> Vendors value their “preferred supplier” status and work hard to protect it by meeting quality, time, and cost targets.<sup>221</sup> Long-term relationships also permit outsourcing teams to build closer and more transparent relationships with vendors.<sup>222</sup>

The last two categories seem to favor drugmakers that can hire large monitoring teams and offer substantial repeat business. Anecdotal evidence suggests that large companies do indeed exploit these advantages.<sup>223</sup> Entities with smaller outsourcing programs reportedly compensate by finding small partners who value their business.<sup>224</sup> However, this strategy can only be effective if small vendors are roughly as efficient as large ones. Anecdotal evidence suggests that this may, in fact, be true.<sup>225</sup>

From a policy standpoint, the key question is how much large drugmakers can save compared to small ones. Anecdotal reports suggest that chemical companies historically earned profits of fifteen to twenty percent. Gains from purchasing power are presumably smaller than this figure. On the other hand, reports that chemical companies successfully forced down margins by five percentage points in the late 1990s suggest that big drugmakers’ purchasing power advantage is at least this large.<sup>226</sup> Better estimates will require detailed research.

*Patent Issues.* Large drugmakers routinely demand full rights to whatever patents may be needed to perform the process. This lets them take the process to whichever manufacturer offers the lowest price.<sup>227</sup>

**Social Challenges:** Because process development is extremely expensive, innovation institutions must be chosen for their ability to contain costs. Institutions should also be able to elicit widely scattered expertise. Agency problems on the researcher side appear to be significant but manageable.

## 7. Phase I Trials<sup>228</sup>

Cost	
Out-of-Pocket	<p>\$15.2 million (DiMasi)</p> <p>\$0.6 – 1.6 million (PPPs)</p>
Time	
To Next Stage	<p>21.6 months. (DiMasi)</p> <p>12-30 months. (PPPs)</p>
Risk	
Transition to Next Stage	<p>71% (DiMasi)</p> <p>70 - .75% (PPPs)</p>

Phase I clinical trials are used to determine safe doses and identify side effects. They are typically performed on twenty to eighty healthy volunteers.<sup>229</sup> Sub-issues include:

*Bioavailability.* Companies need to measure how much active ingredient reaches the bloodstream. The measurements provide a baseline for extending test results to later changes in dose, composition, delivery method, and manufacturing processes.<sup>230</sup>

*Toxicity and Dose Size.* Companies need to confirm what doses patients can tolerate in the short term.<sup>231</sup>

*Data Needed to Design for Further Studies.* Companies gather information about absorption, distribution, metabolic effects, and excretion.<sup>232</sup> In some cases, these tests can yield valuable early information about a drug's efficacy.<sup>233</sup>

Commercial drugmakers have extensive experience purchasing and administering clinical trials for the developed world. However, scientific<sup>234</sup> and regulatory<sup>235</sup> considerations suggest that clinical trials must normally be performed where the drug will be used. Commercial drugmakers have very little capacity or experience administering human trials in LDCs. Furthermore, they are politically reluctant to assume this role for fear of being labeled “exploitative.”<sup>236</sup> For this reason, their participation is usually limited to providing advice.<sup>237</sup> By contrast, PPPs have aggressively developed their capacity to conduct clinical trials in LDCs. Government agencies, private-public partnerships, and local governments possess significantly more expertise in these areas than commercial drugmakers.<sup>238</sup>

**Agency Problems.** Sponsors must design, perform, and interpret Phase I tests. When sponsors outsource these activities to large drugmakers and/or researchers, agency problems can occur at each stage of the process:

*Designing Tests.* Drugmakers possess valuable specialized information about FDA practices, including the ability to predict which studies are likely to satisfy agency regulators. This suggests that they may be able to design tests that meet FDA requirements at lower cost. The size of this advantage is unclear, since FDA and NIH routinely help applicants design trials.<sup>239</sup> Drugmakers' specialized

knowledge of FDA practices is irrelevant to neglected disease research in cases where sponsors seek regulatory approval outside the US.

Drugmakers also possess specialized knowledge about economic factors such as size of potential markets, the feasibility of differentiating their compound from competing products, and the level of proof needed to persuade insurers to purchase the drug.<sup>240</sup> Drugmakers routinely use this commercial information to shape Phase I test designs. Examples include (a) cutting costs through strategic decisions to limit testing to a handful of symptoms,<sup>241</sup> and (b) expanding tests to gain early information about a drug's potential efficacy.<sup>242</sup> This type of commercial information is almost entirely irrelevant to neglected disease research.

*Performing Tests.* Drugmakers typically outsource Phase I tests for rich nation diseases to physicians either directly or through contract research organizations.<sup>243</sup> Because test protocols leave relatively little room for discretion or creativity, sponsors have substantial ability to monitor and control the tests so long as researchers remain reasonably honest. However, outright fraud can be hard to detect. Historically, there have been several scandals in which clinical researchers fabricated data to avoid work or suppressed unfavorable test results.<sup>244</sup>

*Interpreting Tests.* The goal of Phase I trials is to produce data that can be analyzed by any competent statistician. While this transparency suggests that agency problems should be minimal, the argument is limited by the fact that Phase I trials are so small that adverse events in individual patients can sometimes determine a drug's future.<sup>245</sup> Researchers will almost certainly possess additional, unreported information about these cases. Drugmakers also have specialized information about the regulatory process. This may give them superior ability to judge whether drugs that encounter adverse outcomes in Phase I can be rehabilitated through suitably designed follow-up testing.<sup>246</sup>

**Efficient Procurement.** In rich nations, it is reasonable to think that large drugmakers can use their superior buying power to purchase Phase I testing services at a discount. This advantage, if it exists at all, is irrelevant for tests conducted in LDCs.

**Eliciting Information.** Many Phase I tests focus on compounds that have never been tested before. For this reason, existing stores of human knowledge have limited utility. This simple argument is limited by the fact that (a) other researchers may have performed earlier tests on similar compounds, and (b) the prospects for success may depend on non-scientific information about markets or regulatory practices. Industry interviews suggest that knowledgeable observers often disagree about whether a drug that has survived Phase I screening will succeed in Phases II and III.<sup>247</sup>

**Principal Social Challenges.** Because clinical testing is extremely expensive, innovation institutions must be chosen for their ability to contain costs. For rich nation diseases, agency problems frequently exist because drugmakers and/or researchers possess specialized information about whether a drug is likely to succeed. However,

these information advantages and agency problems tend to be much less pronounced for neglected diseases.

## 8. Phase II Trials<sup>248</sup>

Cost	
Out-of-Pocket	\$23.5 million (DiMasi)  1.2 - 3.4 million (PPPs)
Time	
To Next Stage	2.1 Years (DiMasi)  1-5 years (PPPs)
Risk	
Transition to Next Stage	0.44 (DiMasi)  0.5-.75 (PPPs)

Phase II trials are designed to obtain data on short-term safety as well as limited information about efficacy.<sup>249</sup> Tests typically involve 100 to 300 patients suffering from the targeted disease.<sup>250</sup> In principle, sponsors can ask the FDA to grant accelerated approval based on Phase II results.<sup>251</sup> However, this is seldom done because such drugs must still meet post-approval clinical trials that can be hard to satisfy.<sup>252</sup>

In the developed world, drugmakers routinely outsource Phase II trials to competing contract vendors.<sup>253</sup> Government agencies also support some Phase II testing.<sup>254</sup> Drugmakers have very little experience or interest in conducting Phase II tests in LDCs.<sup>255</sup> US and European governments have created most of the Phase II capacity in Africa, Asia, and South America.<sup>256</sup>

**Efficient Procurement.** Outsourced contract research appears to be competitive.<sup>257</sup> LDCs have less clinical trials capacity and may be, to that extent, less competitive.

**Agency Problems.** Drugmakers and contract researchers possess significant specialized information about designing, performing, and interpreting Phase II tests. This information probably allows them to perform tests at lower cost and/or more efficiently than outside sponsors:

*Designing Tests.* Drugmakers possess specialized scientific, marketing, and regulatory information that allows them to design cost-effective Phase II trials. On some occasions, drugmakers may trim testing costs to a bare minimum. On others, they may pursue ambitious tests designed to accelerate development<sup>258</sup> or to enhance eventual market acceptance.<sup>259</sup> These choices make Phase II trial costs enormously variable. According to DiMasi *et al.*, Phase II tests have a mean cost of \$23.5 million but a standard deviation of \$22.1 million.<sup>260</sup>

*Performing Tests.* Drugmakers usually outsource Phase II tests for rich nation diseases.<sup>261</sup> Because test protocols leave little room for discretion or creativity, agency problems are probably manageable. However, outright fraud may be hard to detect. In the developed world, drugmakers may use their superior buying power and large staffs to extract additional value from outsourced research. This advantage does not exist in LDCs.

*Interpreting Tests.* In principle, any competent statistician can evaluate Phase II data. This conclusion is supported by anecdotal evidence that drug companies appoint neutral evaluators to audit their own in-house R&D projects.<sup>262</sup> With increased trial size, researcher knowledge of individual cases is less important in Phase II than in Phase I.<sup>263</sup>

*Interacting With FDA.* The FDA routinely holds an End-of-Phase-II meeting with drugmakers to agree on the remaining tests needed demonstrate efficacy and obtain regulatory approval. Drugmakers see the meeting as extremely important and may have significant specialized knowledge about how to prepare for it.<sup>264</sup>

**Eliciting Information.** Many Phase II tests focus on compounds that have never been tested before. For this reason, existing stores of human knowledge have limited utility.

**Social Challenges.** Because clinical testing is extremely expensive, innovation institutions must be chosen for their ability to contain costs. For rich nation diseases, agency problems frequently exist because drugmakers and/or researchers possess specialized knowledge about how to design, conduct, and interpret Phase II trials. This advantage is largely irrelevant when sponsors conduct trials in LDCs and/or decide not to seek FDA approval.

## 9. Phase III Trials<sup>265</sup>

Cost	
Out-of-Pocket	<p>\$125 million (DiMasi)</p> <p>\$86 million (<i>Wall Street Journal</i>)</p> <p>\$12.2 – 51.0 million (PPPs)</p>
Time	
To Next Stage	<p>2.5 years (DiMasi)</p> <p>2 – 4 (PPPs).</p>
Risk	
Transition to Next Stage	<p>68.5% (DiMasi)</p> <p>65 – 68% (PPPs)</p> <p>&lt; 50% (vaccines)</p>

Phase III trials are designed to gather precise information on effectiveness for specific indications, search for rare and unknown side effects, optimize delivery methods and doses, and provide evidence for product labels. Trials typically include several hundred to several thousand subjects and are far more expensive than other research.<sup>266</sup> Although most clinical trials are commercial, government agencies also possess substantial capacity to conduct and manage trials.<sup>267</sup>

Thailand and other LDCs have recently hosted several high quality Phase III studies.<sup>268</sup> However, most drugmakers have little or no experience managing trials in LDCs.

**Eliciting Information.** Many Phase III tests focus on compounds that have never been tested before. For this reason, existing stores of human knowledge tend to have limited utility.

**Agency Problems.** Drugmakers and contract researchers possess significant

specialized information about designing, performing, and interpreting Phase III trials. This information permits them to perform tests at lower cost:

*Designing Tests.* Drugmakers possess specialized scientific, marketing, and regulatory information that allows them to design cost-effective Phase III tests.<sup>269</sup> These choices make Phase III trials enormously variable.<sup>270</sup> Anecdotal evidence suggests that successful negotiations with FDA can drastically reduce costs, most notably by persuading regulators to accept one controlled study instead of two.<sup>271</sup>

Drugmakers' specialized information is largely irrelevant when tests are conducted in LDCs. PPPs typically have much better ability to design tests that will persuade procurement agencies to purchase new drugs.<sup>272</sup>

*Performing Tests.* Sponsors find it relatively easy to monitor routinized testing. For this reason, agency problems are likely to be minimal. However, scientific

fraud may be hard to detect. Drugmakers typically know much less about conducting tests in LDCs than local health authorities and/or NGOs do.<sup>273</sup>

*Evaluating Tests.* Phase III trials often generate one million case reports.<sup>274</sup> In this context, researcher knowledge of individual patients is relatively unimportant. Nevertheless, a drug’s future may sometimes depend on a handful of adverse events. Researchers may have a substantial information advantage in such cases.

**Efficient Procurement.** Phase III trials are usually outsourced to contract workers and appear to be competitively supplied.<sup>275</sup> LDCs have less clinical trials capacity and may be, to that extent, more oligopolistic.

**Social Challenges.** Because clinical testing is extremely expensive, innovation institutions should be chosen for their ability to contain costs. For rich nation diseases, agency problems frequently exist because drugmakers and/or researchers may possess specialized knowledge about how to design, conduct, and interpret Phase III trials. This advantage is largely irrelevant when sponsors conduct trials in LDCs and/or decide not to seek FDA approval.

## 10. FDA Approvals<sup>276</sup>

<b>Cost</b>		
Out-of-Pocket		~ \$3 million
<b>Time</b>		
To Next Stage		10 months (expedited)  6-18 months (DiMassi, PPPs)
<b>Risk</b>		
Transition to Next Stage		90-95%

FDA approval is based on a written New Drug Application (“NDA”) containing summaries, individual study reports, and tabulated data on up to 50,000 patients.<sup>277</sup> The process culminates in a hearing at which the FDA can grant, reject, or defer the application pending further information. Large drugmakers typically invest several man-years in preparing for hearings, although smaller companies make do with less.<sup>278</sup> Government agencies also provide limited advice on how to draft a successful NDA.<sup>279</sup>

**Agency Problems.** In practice, commercial drugmakers seldom if ever outsource relations with FDA regulators.<sup>280</sup> The reason almost certainly involves agency problems. First, the approval process requires a high degree of creativity and discretion, is difficult to monitor, and has large penalties for failure. Second, agents must possess highly specialized knowledge. Industry representatives report (a) that FDA’s willingness to approve drugs varies over time and has a strong political component,<sup>281</sup> (b) that success requires a detailed knowledge of FDA procedures,<sup>282</sup> and (c) that detailed knowledge of individual regulators is useful.<sup>283</sup> Available evidence suggests that such knowledge is extremely valuable. During the late 1990s, experienced sponsors were three times likelier to have their NDAs approved than other companies.<sup>284</sup>

The case is different once a drug is rejected. The fact that drugmakers sometimes purchase rights to rejected drugs suggests that outsiders can obtain relatively accurate information about a drug’s regulatory status and scientific prospects.<sup>285</sup> On the other hand, purchasers must still possess significant specialized knowledge about scientific risk, FDA receptivity, and potential markets.<sup>286</sup> It is not clear how much of this information is available to PPPs. Specialized knowledge is probably less valuable for neglected diseases where rich nation markets – and in some cases FDA approval – are less relevant.

**Efficient Procurement.** Like their commercial counterparts, PPPs are overwhelmingly likely to handle FDA negotiations in-house. Sponsors will presumably pay normal markups for this work.

**Eliciting Knowledge.** Approval hearings are tightly focused on existing test results. For this reason, outside scientific information is largely irrelevant.

**Social Challenges.** Agency problems are significant. Like their commercial counterparts, PPPs will probably conduct most FDA negotiations in-house.

## 11. Manufacturing<sup>287</sup>

<b>Cost</b>		
Fixed Cost		\$100-150 million
APIs		\$500 per kg.
Per-Dose Cost of Finished Drugs		20% of total product price

Manufacturing costs are roughly comparable to R&D expenditures for most commercial drugs.<sup>288</sup> Manufacturing issues are particularly pressing for vaccines and biopharmaceuticals, which must be made using the same techniques that will be employed in full-scale production. This

means that sponsors must often invest in full-scale facilities before test outcomes are known.<sup>289</sup>

**Efficient Procurement.** Ten to fifteen percent of intermediates are currently outsourced and this figure is expected to grow. Consultants predict that some drugmakers will eventually outsource all of their manufacturing needs.<sup>290</sup>

As noted in Section III.C.6, contract manufacturing is extremely competitive. By comparison, competition for biologics is hindered by regulations that make it difficult for manufacturers to use the same plant and equipment for multiple products.<sup>291</sup> Despite this, contract biopharmaceutical manufacturing is also growing.<sup>292</sup>

*Inefficient Outsourcing.* Asian companies reportedly charge five percent less than rich nation manufacturers.<sup>293</sup> Despite this dramatic cost advantage, drugmakers are still reluctant to outsource to Asia because of fears that their intellectual property will be stolen. For this reason, outsourcing is usually limited to situations where (a) market forces demand stringent cost containment, (b) production involves unfamiliar

technologies, (c) production runs are small, (d) demand cannot be met without building additional in-house capacity, (e) production involves early stage intermediates instead of a final product, (f) production involves drugs whose patents are about to expire, or (g) production involves drugs whose patents have already expired.<sup>294</sup> These restrictions are likely to become steadily less important as Asian patent laws change and Asian companies become more skillful at meeting Western regulatory requirements.<sup>295</sup>

**Agency Problems.** Because manufacturing is extremely expensive, innovation institutions must be chosen for their ability to contain costs. As noted in Section III.C.6, drugmakers frequently use aggressive monitoring, second-sourcing,<sup>296</sup> competitive bids, and the prospect of long-term repeat business to ensure that outside vendors deliver value.

## 12. Phase IV & Off-Label Use Trials

Companies typically devote about one-fourth of their total R&D budget – about \$140 million – to Phase IV and Off-Label Use trials.<sup>297</sup> These programs are needed, *inter alia*, to (a) keep FDA approval in place for as long as the product is sold,<sup>298</sup> and (b) to extend existing FDA approvals to new populations and/or uses. Despite this, two to three percent of all drugs are ultimately removed from the market because of side effects.<sup>299</sup> Post-approval R&D includes:

*Phase IV Studies.* Companies perform ongoing studies to monitor long term morbidity, detect adverse outcomes, and focus on particular populations (*e.g.*, children, the elderly, pregnant women) not previously included in Phase III trials.<sup>300</sup> Some, but not all of these tests are required by the FDA

*Off-Label Studies.* Companies may conduct studies to demonstrate a new drug's superiority over competing products or to document new uses.<sup>301</sup>

*Routine Reporting Requirements.* Companies must report adverse suspected events<sup>302</sup> as well as changes in chemistry, manufacturing, or production controls. New labels, promotional materials, or major manufacturing changes must be approved in advance.<sup>303</sup>

Drugmakers have extensive specialized knowledge in meeting these requirements. Some government agencies also provide advice in conducting off-label studies.<sup>304</sup>

## 13. Marketing and Distribution.

Rich nation pharmaceutical marketing exhibits massive economies of scale.<sup>305\*</sup> This factor – together with superior access to financing<sup>306</sup> – has traditionally forced biotech companies to partner with large drugmakers.<sup>307</sup> Recently, however, some biotechs have begun purchasing marketing services from outside vendors. Reportedly, the strategy does not yield significant savings.<sup>308</sup> Nevertheless, the existence of such practices suggests that any cost penalty is modest.

Commercial marketing capabilities are largely irrelevant to neglected diseases, since drugmakers possess little or no distribution capacity within LDCs.<sup>309</sup> Instead, distribution tends to be managed by a combination of public sponsors (WHO, NGOs)<sup>310</sup> and local shops and markets.<sup>311</sup> Knowledgeable commentators claim that PPPs know much more than commercial drugmakers about persuading sponsors to purchase new products.<sup>312</sup>

### D. Private-Public Partnerships

**History.** Private-public partnerships (“PPPs”) first emerged in the mid-1990s as an initiative of the Rockefeller and Gates Foundations.<sup>313</sup> As of 2004, sponsors had committed at least \$1.2 billion to PPPs.<sup>314</sup> Although PPPs feature a bewildering mix of goals and strategies, roughly two-dozen of them currently concentrate on drug R&D.<sup>315</sup> These PPPs will need between \$1.2 and \$2.2 billion in new funding commitments to keep their existing drug development programs on track through 2007.<sup>316</sup>

Drug development PPPs are still evolving, with clinical trials just beginning and actual drugs some years off.<sup>317</sup> There is still little consensus on whether, when, or why PPPs work.<sup>318</sup>

**Strategic Investing.** Strategic investing strategies subsidize commercial programs that have either stalled or would not otherwise exist.<sup>319</sup> Forty-one percent of PPPs are sufficiently interested in strategic investing to have performed formal market studies.<sup>320</sup> Possible subsidies include up-front funding of particular research phases, profit or sales volume guarantees, cost sharing, in-kind assistance with regulatory bodies,<sup>321</sup> and grants to private R&D programs.<sup>322</sup> Some agreements require the corporate partner to reimburse subsidies if it later decides to sell the drug commercially.<sup>323</sup>

Because the private sector invests significant resources, PPPs have only limited influence over the design and direction of R&D.<sup>324</sup> Companies can and do refuse to tailor drug research to particular patient groups, countries, or price needs,<sup>325</sup> perform clinical trials that do not meet FDA standards,<sup>326</sup> or target politically sensitive populations (*e.g.* pregnant women).<sup>327</sup>

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\*Drugmakers that direct-market products to doctors must hire thousands of salesmen. Once this network exists for one product, the incremental cost of marketing additional drugs is generally small.

Strategic investing is wasteful to the extent that PPPs end up subsidizing projects that the private sector is willing to fund on its own. In this case, public money simply replaces (“crowds out”) private funds with no net increase in funding. The problem is compounded by the fact that (a) private firms have a powerful incentive to overstate the need for subsidies, and (b) PPPs have very little independent information about the project’s attractiveness to investors. By itself, the fact that commercial research has stopped means little. Some companies let projects sit on the shelf for five years before resuming R&D.<sup>328</sup>

**Portfolio Management.** Many PPPs try to replicate private sector portfolio management techniques. Two-thirds (64%) have pursued this strategy to the extent of creating a formal scientific blueprint, often including a portfolio plan. PPPs pursuing portfolio management strategies typically outsource, pay for, and control all work. Private partners receive their reward in the form of up-front payments instead of patent rights.<sup>329</sup>

Table 2 summarizes worldwide PPP R&D efforts. At the level of individual programs, some PPPs have assembled substantial portfolios of up to twenty-five projects.<sup>330</sup> However, other PPP portfolios are still too small to meet announced development targets.<sup>331</sup> For now, MMV, DNDi<sup>332</sup> IAIVI<sup>333</sup> and IOWH appear to have the largest staffs and most rigorous portfolio management practices.<sup>334</sup> Despite this, some commercial observers complain that PPP research is “not being done in a rigorous enough way to succeed.”<sup>335</sup>

**Table 2:**  
**PPP R&D Programs<sup>336</sup>**

	Pre-Clinical	Phase I	Phase II	Phase III
Vaccines	19	8	2	0
Drugs	26	8	5	8
Total	47	16	7	8

To date, most PPPs have focused on quick results<sup>337</sup> in an effort to demonstrate their effectiveness to funders and the

general public as soon as possible.<sup>338</sup> These PPPs usually focus on modifying known compounds and/or adapting existing drugs to treat new diseases.<sup>339</sup> Furthermore, almost all PPPs avoid early-stage research.<sup>340</sup>

In the long run, current investments in basic research are too small to keep PPP portfolios full.<sup>341</sup> The problem is most urgent for (a) tuberculosis, and (b) trypanosomiasis, Chagas disease, leishmaniasis, and other diseases for which rich nation markets are limited.<sup>342</sup> Extending PPP programs to include more upstream research will be expensive.<sup>343</sup>

**Ensuring Access.** Commercial pharmaceutical companies plan for distribution early in the R&D cycle. Some PPPs similarly gather information about whether public sponsors are likely to purchase a new product and/or build “access systems” to deliver drugs to patients. One-third (29%) of PPPs are sufficiently committed to these issues to have created an access plan.<sup>344</sup> PPPs use various contract clauses to promote access:

*Open Price.* Many contracts either ignore price<sup>345</sup> or constrain it only weakly, for example by undertaking to agree on a “reasonable” profit at some future date.<sup>346</sup> Alternatively, many contracts announce detailed price terms but then go on to say that the PPP’s only recourse if the private entity reneges is to develop, manufacture, and sell the product itself.<sup>347</sup> Such price guarantees are almost entirely illusory.

*Tiered Pricing.* Existing access plans usually depend on commercial partners to manufacture and distribute the drug. Most agreements provide for *tiered pricing* in which commercial partners are allowed to maintain their patent monopoly in rich nations in exchange for offering lower prices to LDCs. These agreements come at a cost, since suppressed competition in rich nation markets usually means that there will be fewer competitors able to manufacture drugs for LDCs.\* Within LDCs, prices may be further subdivided into a low “public sector price,”<sup>348</sup> an intermediate “social marketing” price designed to expand access for poor consumers,<sup>349</sup> and a “private sector distribution price” for middle- and upper-class patients.<sup>350</sup>

*Reasonable Price Terms.* Many contracts provide that manufacturers will deliver products to endemic countries at a “reasonable price.” Sometimes, this price is defined in terms of an explicit mark-up<sup>351</sup> or agreed sales volume.<sup>352</sup> More often, it is defined in terms of inherently ambiguous standards including (a) the private partner’s investment, worldwide earnings, and the relative size of developing markets; (b) the goal of reaching “the widest and most rapid deployment possible,”<sup>353</sup> and (c) the manufacturer’s right to earn a reasonable profit,<sup>354</sup> or “minimum return on sales.”

*Second Sourcing.* In principle, PPPs can constrain prices by reserving the right to purchase drugs from “second-source” manufacturers. This right usually takes the form of a royalty-free license to produce and distribute the drug (a) throughout the LDC,<sup>355</sup> or (b) for “social marketing” and “public sector” uses within particular LDCs.<sup>356</sup> Some PPPs have said that they will pay manufacturers to produce drugs under contract.<sup>357</sup>

**Other Missions.** Although strategic investment and portfolio management are the most common PPP missions, they are not the only ones. Additional justifications include:

*Expertise.* PPP staff provide valuable information to funders who lack in-house drug discovery expertise.<sup>358</sup>

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\* Even if the private partner promises to sell the drug to LDCs “at cost,” competing firms may be able to manufacture the compound more cheaply. Furthermore, it may be difficult for PPPs to confirm that drugs are actually being sold at cost even when accounting data are available. Competition achieves this result automatically.

*Exploiting In-Kind Resources.* PPPs provide a channel for absorbing in-kind contributions from the private sector<sup>359</sup> and trading on intangible public sector assets like public relations, proof of technology, data, training, technical know-how, introductions to new markets,<sup>360</sup> know-how in obtaining approvals from sponsors,<sup>361</sup> data,<sup>362</sup> and introducing products to researchers.<sup>363</sup>

*Education and Advocacy.* Many PPPs consider education and advocacy “core activities.”<sup>364</sup>

*Fund Raising.* All PPPs practice “communications advocacy” to fund their own programs.<sup>365</sup>

*Tool & Infrastructure Development.* Some PPPs focus on building unique assets for conducting and accelerating research.<sup>366</sup> Projects range from building clinical trials capacity<sup>367</sup> to funding basic research tools in an effort to accelerate R&D.<sup>368</sup>

*Building LDC Scientific and Industrial Capacity.* Some PPPs assign high priority to building capacity in LDCs and involving diverse LDC stakeholders on social justice grounds.<sup>369</sup> These goals may sometimes conflict with cost-effectiveness.

Table 3:  
Portfolio-Based PPPs<sup>370</sup>

<p>International AIDS Vaccine Initiative (IAVI)<sup>371</sup></p>	<p><b>Founded:</b> 1996.</p> <p><b>Funding:</b> IAVI has current commitments of \$350 million and hopes to have \$655 million by 2008. IAVI uses 75% of its budget to support promising vaccine candidates.</p> <p><b>Portfolio:</b> IAVI was the first PPP to focus on vaccine development. It is current participating in five development partnerships. IAVI and its partners are currently conducting clinical trials in Uganda, Kenya, South Africa, the UK, Belgium, Germany, Switzerland, and the US. IAVI currently has twenty preclinical drugs, five Phase I drugs, and one Phase II drug in its portfolio.</p> <p><b>Strategies:</b> IAVI seeks to own or co-own all vaccines in which it invests. Small biotechs do the work under contract in cooperation with one or more academic research centers. Commentators speculate that IAVI may have to continue development through the entire pipeline unless it can persuade major vaccine providers to assume development. IAVI's eighty employees include experts on each stage of the drug development process, including manufacturing.</p>
<p>International Partnership for Microbicides<sup>372</sup></p>	<p><b>Founded:</b> 2002</p> <p><b>Funding:</b> IPM has commitments of \$230 million and hopes to spend a total of \$775 million over the next five years.</p> <p><b>Portfolio:</b> IPM had fourteen microbicides in clinical trials as of 2003. Five compounds were scheduled to enter Phase III trials in 2004.</p> <p><b>Strategies:</b> Unusually for a PPP, IPM is developing its own network of clinical trial sites. IPM currently has three preclinical and twelve Phase I drugs in its portfolio.</p>
<p>Medicines for Malaria Venture<sup>373</sup></p>	<p><b>Founded:</b> 1999.</p> <p><b>Funding:</b> MMV has commitments of 107 million. Its ultimate goal is to spend \$30 million per year while attracting comparable in-kind support from industry. Outsiders estimate that MMV may have to spend between \$100 and \$200 million to bring some of its drugs through to approval.</p> <p><b>Portfolio:</b> MMV was the first PPP to pursue drug development using industry-style portfolio methods. MMV estimates that a portfolio of roughly two dozen projects would be sufficient to deliver one new antimalarial every five years. Its current portfolio includes twenty-one candidates, including eight completely new targets. Ten compounds are currently under development, some of which have entered Phase III trials. MMV's Scientific Advisory Board reviews projects annually for milestones and continued competitiveness with other projects.</p>

	<p>Success indicators include size and quality of the pipeline and adherence to industry norms on pipeline progression. MMV has terminated four projects to date. MMV currently has six pre-clinical, three Phase I, one Phase II, and two Phase III drugs in its portfolio.</p> <p><b>Strategy:</b> MMV issues a general call for proposals every two years; 100 are received and about ten are accepted. MMV purchases clinical trial services from outside organizations. MMV works with major pharmaceutical companies wherever possible because of their expertise in manufacturing, regulatory approval, and distribution. MMV does not own compounds, but insists on exclusive marketing rights for low income countries.</p>
Malaria Vaccine Initiative <sup>374</sup>	<p><b>Founded:</b> 1999</p> <p><b>Funding:</b> MVI has spent \$43 million since 1999. It recently received \$100 million to conduct clinical trials of four leading candidates in its portfolio. MVI has nine pre-clinical, three Phase 1, and three Phase II drugs in its portfolio.</p> <p><b>Portfolio:</b> MVI currently has twenty vaccine candidates in development. Eight of these candidates are in Phase I or Phase II trials.</p> <p><b>Strategy:</b> MVI invests its budget in development partnerships with industry, biotech firms, government agencies, and academia.</p>
Global Alliance for Tuberculosis Drug Development <sup>375</sup>	<p><b>Founded:</b> 2000</p> <p><b>Funding:</b> Global Alliance has committed funds of \$42.2 million; the Global Alliance’s budget was expected to reach \$14.4 million by 2004. Most of it is spent on funding outsourced R&amp;D by outside contract research organizations, institutes, and companies.</p> <p><b>Portfolio:</b> Global Alliance currently has ten compounds in lead identification, lead optimization, or preclinical development. It ultimately hopes to participate at all phases of drug development from pre-clinical testing through manufacturing and distribution. Global Alliance reportedly needs five or six additional compounds to round out its portfolio. It also invests in “platform technologies” (e.g. animal models), advocacy, and patient outreach. Global Alliance currently has nine pre-clinical and one Phase II drug in its portfolio.</p> <p><b>Strategy:</b> Global Alliance sees itself as an “incubator” that encourages companies to make what are basically profit-maximizing decisions to invest in R&amp;D. Subsidies include staged funding, expert scientific and management guidance, and limited infrastructure support (e.g., project management and legal services). Global Alliance acquires most of its drug candidates under license. Companies retain full rights in rich nation markets and/or spin-off applications for unrelated diseases.</p>
Areas Global Tuberculosis Vaccine Foundation (formerly	<p><b>Founded:</b> 1999.</p> <p><b>Funding:</b> Areas has commitments of \$107.9 million.</p> <p><b>Portfolio:</b> Areas currently has four pre-clinical and two Phase I drugs in its portfolio. Areas plans to conduct Phase I, II, and III trials of</p>

<p>Sequella Global TB Vaccine Foundation)<sup>376</sup></p>	<p>several tuberculosis drugs over the next decade. It also hopes to develop and manufacture at least one new tuberculosis vaccine within ten years.</p> <p><b>Strategy:</b> Areas is currently developing Phase III trials capacity in South Africa.</p>
<p>Drugs for Neglected Diseases Initiative<sup>377</sup></p>	<p><b>Founded:</b> 2003.</p> <p><b>Funding:</b> DNDi currently has commitments of \$30 million. It plans to spend \$250 million over twelve years.</p> <p><b>Portfolio:</b> DNDi plans to produce six or seven drugs over the next twelve years. Early research will focus on relatively simple projects including (a) partially tested drug candidates that have been abandoned as non-commercial, and (b) new uses for existing drugs. In the long run, DNDi will conduct more ambitious R&amp;D aimed at finding new lead compounds. The work will either be done in-house or through outside partners.</p> <p><b>Strategy:</b> DNDi was the first PPP to focus on African Trypanosomiasis, leishmaniasis, Chagas, and other diseases for which rich nation markets are trivial. DNDi hopes to “mirror the structure of a drug development management team in private industry, while outsourcing most R&amp;D activities from discovery through . . . clinical trials.” Manufacturing will “rely on existing worldwide drug production capacity, especially in the South.” DNDi expects industry to donate access to expertise, compound libraries, and R&amp;D facilities.</p> <p>DNDi will dedicate its work to the public domain as a “general rule.” However, DNDi reserves the right to seek patents (a) to earn income, or (b) to trade for existing drugs, proprietary compounds, and research tools. DNDi’s licenses will normally be non-exclusive and limited to specific “targeted indications.” It currently has four discovery phase, one preclinical, and four Phase III drugs in its portfolio.</p>
<p>Institute for OneWorld Health<sup>378</sup></p>	<p><b>Founded:</b> 2000.</p> <p><b>Funding:</b> iOWH currently has commitments of \$11.3 million.</p> <p><b>Portfolio:</b> Current iOWH projects include Phase III trials of an existing off-patent antibiotic (paromomycin) for a new application (visceral leishmaniasis). iOWH also plans to develop the patented compound CRA-3316. Celera has donated rights to the drug for all parasitic diseases in all markets, but may benefit if iOWH’s work reveals non-parasite applications. iOWH will perform Phase III trials for the drug and seek regulatory approval in India.</p> <p><b>Strategy:</b> iOWH licenses promising drug candidates that would not normally attract private investment funds at the pre-clinical or clinical stage. It then pays for development. Once drugs are approved, IOWH plans to outsource manufacturing and distribution to LDC corporations.</p>

## E. Do High Drug Prices Matter?

*How Much Can Drug Prices Be Reduced?* Manufacturing constitutes roughly one-fifth of typical drug costs.<sup>379</sup> The rest is due to R&D, marketing, sales, and profit. In principle, therefore, unpatented drugs can be manufactured at discounts approaching eighty percent below current cost.\* Evidence from generic<sup>380</sup> and LDC sales<sup>381</sup> are broadly consistent with this estimate. Discounts could be even larger for vaccines,<sup>382</sup> which tend to spread costs over bigger production runs.

*Should Sponsors Promote Access Pricing?* Access pricing offers limited benefits where the sponsor will be required to pay for *both* R&D *and* manufacturing costs. Assuming that patent revenues are exactly equal to the drugmaker's R&D expenses, a rational sponsor would not care whether it paid for research up-front or through after-the-fact patent royalties.† This argument suggests that access pricing may have limited utility for diseases in some Sub-Saharan nations, where foreign aid regularly pays for thirty to fifty percent of healthcare.

Access pricing is considerably more attractive where LDC consumers and governments pay for their own healthcare. Drug purchases account for one-third to one-half of many LDC healthcare budgets.<sup>383</sup> Naively, a fifty percent cut in drug prices could increase real healthcare spending in these countries by 15 to 25%.

In practice, this is almost certainly an overestimate. First, consumers and governments are likely to reallocate part of the savings from lower drug costs to other, non-healthcare needs.<sup>384</sup> Second, price cuts at the factory might not reach consumers because of endemic corruption and markups.<sup>385</sup> Finally, the benefits of access pricing are not evenly distributed. In the simple case where manufacturers can only set a single price, every dollar that the sponsor spends to drive down drug prices will (a) increase the number of poor people who can afford the drug, but also (b) subsidize middle- and upper-class patients, who now pay less. The relative size of these effects depends on wealth distribution. In the extreme case where LDC citizens are either very wealthy or extremely poor, modest price cuts will mostly benefit wealthy patients. Anecdotal evidence suggests that this model may be fairly realistic in some LDC drug markets.<sup>386‡</sup>

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\* The estimate assumes that R&D costs have already been paid for. We address the case where a single sponsor pays for both R&D and manufacturing below.

† This is only true where the sponsor has perfect information about the researcher's R&D costs and the size of the potential market. If the researcher has superior information on these topics, paying in advance may be preferable because it eliminates one unknown (market potential).

‡ Sponsors have a much stronger case for using patents to extract R&D funds from wealthy consumers when drugs are developed to treat rich nation diseases. In this case, allowing LDCs to "free-ride" on rich nation investment reduces typical patent incentives by about two percent. Most commentators argue that the resulting drag on R&D incentives is negligible and ought to be implemented. Jean O. Lanjouw, "Outline of Foreign Filing License Approach" (2004), available at <http://www.cgdev.org/docs/FFLOutline.pdf>. By definition, such strategies do not apply to the neglected diseases discussed in this paper.

“The country needs and, unless I mistake its temper, the country demands bold, persistent experimentation. It is common sense to take a method and try it. If it fails, admit it frankly and try another. But above all, try something.”

-- Franklin D. Roosevelt  
on fighting the Great  
Depression (1932)<sup>387</sup>

## V. Analysis.

This section examines current proposals and suggests additional strategies for using non-patent incentives to develop drugs for neglected diseases. Section A focuses on AdvancedMarkets and similar “end-to-end” solutions that envision a single reward for the entire drug discovery process. Such strategies leave management decisions largely in private hands. Section B focuses on “pay-as-you-go” strategies in which non-profit entities set separate rewards for each stage of the R&D process. Inevitably, these proposals transfer much of the responsibility for deciding which drugs to investigate from private to non-profit managers. Section C discusses how PPPs can be strengthened to support either strategy. Finally, Section D asks what universities and other institutions can do to support neglected disease research.

### A. End-to-End Solutions

In principle, end-to-end solutions can be based on any of the incentives described in Section III.B. In practice, no serious proposal argues that end-to-end systems should be based on, for example, grants or contract research. The reason is that end-to-end solutions entail – by definition – large, infrequent rewards that make agency problems on the researcher side particularly dangerous. This factor limits sponsors to incentives (*e.g.* boosted demand, guaranteed payments) that withhold payment until researchers succeed. Because these mechanisms force sponsors to set reward size in advance, overpayment is almost always a significant risk.

#### 1. Boosted Demand.

Boosted demand argues that increased rich nation funding of sponsors will automatically revive patent incentives for new drugs. Some boosted demand proposals claim that rich nation governments can enhance the effect by announcing that they plan to spend still more money in the future.

**Basic Strategy.** Commercial drugmakers routinely invest in R&D without any formal guarantee (a) that rich nation governments will not cut health agency budgets in the future, or (b) that health agencies will not use their buying power to force prices to unprofitable levels. This behavior is reasonable. Because of political inertia, current government practices could well be a better guarantee of future spending than formal commitments.

**Non-Binding Assurances.** Drugmakers sometimes change *existing* investment based on a government's non-binding assurances that it plans to increase funding *in the future*. This happened during the 1990s, when the British Health Department announced that it would buy a meningitis vaccine if one were developed. In the end, three firms developed products, all of which were purchased.<sup>388</sup> The US is currently using a similar strategy to encourage drugmakers to invest in bioweapons vaccines.<sup>389</sup>

Assurances of future spending are less likely to accelerate investment in neglected disease research, where sponsors must persuade drugmakers to overlook a history of stagnant budgets and low prices. However, assurances may be useful where drugmakers are uncertain about sponsors' attitudes toward particular classes of drugs. Anecdotal evidence suggests that many companies hesitate to invest in AIDS vaccines because they do not know whether sponsors would purchase such a product.<sup>390</sup> Sponsors could remove this obstacle by making internal deliberations more transparent.

**Conclusion.** Boosted demand strategies are certain to work if the "boost" is large enough. However, increased sponsor budgets since the 1990s have done little or nothing to accelerate private investment in new drugs.<sup>391</sup> Foreseeable budget increases are not likely to change this picture.

## 2. AdvancedMarkets.

In 2001, the Gates Foundation asked the Center for Global Development to convene a blue ribbon working group to assess whether an advance purchase commitment could be implemented in practice and whether it would be effective. The working group's "consensus" design is called "AdvancedMarkets."<sup>\*</sup>

**Description.** The AdvancedMarkets proposal would establish a minimum price for the first 200 million treatments of a new vaccine. Sponsors would pay 95% of the cost with the balance coming from LDC co-payments.<sup>392</sup> New vaccines would have to meet pre-announced specifications in order to qualify for the program. An Independent Adjudication Committee ("IAC") would determine when these standards were met.

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\* CGD has reportedly decided to drop the "AdvancedMarkets" in favor of the more generic term "APC" in its final report.

Finally, LDCs could stop purchasing vaccines if a substantially better product appeared on the market and was approved by the IAC.\*

AdvancedMarkets would initially be limited to vaccines. However, proponents argue that similar methods could eventually be used to accelerate commercial development of drugs, diagnostic tests, and medical devices.<sup>393</sup>

**Reward Size.** Despite extensive study, AdvancedMarkets proponents do not say what guaranteed price is needed to elicit development, except that it probably falls between \$15 and \$25 per person immunized.† Payments under the higher price would thus be 167% larger than the lowest price that might work. As explained in Section IV.B.6, sponsors who chose the higher price could expect to overpay by an average of thirty-four percent.

Significantly, AdvancedMarkets proponents do not promise to deliver more refined estimates in the future. They only argue that sponsors should choose a price based, *inter alia*, on “the willingness of sponsors and recipient governments to pay.”<sup>394</sup>

**Post-Guarantee Manufacturing.** AdvancedMarkets payments would end after the first 200 million doses were sold. At this point, drugmakers would be required to sell vaccines at an “agreed formula related to the cost of production.”<sup>395</sup> AdvancedMarkets provides two possible versions of what would happen next. In one scenario, drugmakers could escape their manufacturing obligation by giving sponsors the right to make the compound themselves.<sup>396</sup> This would render the obligation illusory. In a second scenario, drugmakers that stopped manufacturing would be required to pay liquidated damages.<sup>397</sup> Sponsors could use these funds to acquire the drug from other sources. In this case, the original drugmaker’s obligation would not be illusory, although the prospect of liquidated damages might reduce its incentive perform R&D in the first place.

*Adjusting the Reward.* As noted in Section III.B.3, one way to prevent overpayments under a guaranteed reward system is to choose a low price and then raise it if drugmakers fail to respond. AdvancedMarkets rejects this option on the ground that it would create “additional complexity ... at the outset.”<sup>398</sup> This judgment may reflect the limited power of such strategies in an era of rapidly growing R&D costs. Nevertheless, AdvancedMarkets’ caveat (“at the outset”) reserves the right to adjust prices at a later date.

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\* As explained below, drugs that offered only incremental improvement over existing products would not qualify for AdvancedMarkets subsidies.

† AdvancedMarkets variously proposes a range of \$15 to \$25 for each of the first 200 million doses or \$2 - 3 billion in present value. The estimate corresponds to average sales from “the upper quartile of market sizes for new medicines introduced in the early 1990s”; use of the upper quartile is justified on the ground that vaccines are “more technically challenging . . . than other medicines.” Proponents argues that prices for a malaria vaccine could be set near the lower (\$15) end of the range based on preliminary evidence of a \$700 million market for rich nation tourists and military personnel. AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 56.

Ultimately, the feasibility of adjusting the reward over time turns on a political and moral judgment about how much delay is acceptable. Proponents argue that AdvancedMarkets should be terminated if “no substantial progress” is made in thirty years.<sup>399</sup> Depending on what is meant by “substantial progress,” failure might be apparent if drugmakers still had no projects in their pipelines after fifteen to twenty years. Such delays are probably at the outer limit of political acceptability.

Finally, AdvancedMarkets would not give its IAC discretion to adjust prices upward if new drugs exceeded specifications<sup>400</sup> or downward if drugmakers’ R&D costs were reduced by technology changes or government subsidies.<sup>401</sup> This may reflect a judgment that letting the IAC adjust rewards *ex post* will produce fewer savings than it is likely to cost in the form of aggravated agency problems.

*Rewarding Second Generation Products.* As noted in Section III.B.2, the social value of new vaccines steadily decreases as more people are vaccinated. For this reason, previous guaranteed price proposals have argued that the first developer should receive “a more substantial reward” than successors.<sup>402</sup> However, setting this differential requires detailed knowledge of (a) when follow-on products are likely to appear, and (b) the quality improvements they are likely to deliver. AdvancedMarkets avoids these difficulties by setting a single guaranteed price, but then lets second-generation drugs capture the market if they arrive before subsidies are exhausted.<sup>403</sup> In effect, the system encourages drugmakers to deliver second-generation products as soon as possible.

The AdvancedMarkets solution also encounters problems in cases where a second-generation drug builds on first generation technologies. In this case, owners of first generation patents can block subsequent entrants. This is not a problem for conventional patent systems where patent owners can agree to charge a higher price for the improved product and split the additional revenues. In AdvancedMarkets, however, the price is fixed. This means that first-generation drugmakers may decide to block improved products unless and until the sponsor pays “monopoly-size bonuses.”<sup>404\*</sup>

**Commitment Strategies.** AdvancedMarkets uses an Independent Advisory Committee (“IAC”) to ensure that sponsors do not renege on their commitments.<sup>405</sup> Since sponsors could presumably ignore an IAC’s decisions, the mechanism ultimately depends on judicial enforcement. The principal advantage of IACs over courts seems to be (a) specialized medical expertise, and (b) a perception that private drugmakers are unlikely to participate in systems that require them “to take a UN agency to court . . .”<sup>406</sup> Experience with semiautonomous government bodies (*e.g.* central banks<sup>407</sup>) suggests that IACs would be an effective commitment strategy.

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\* AdvancedMarkets could fix the problem by requiring first-generation drugmakers to license their technologies to second-generation manufacturers that participated in the program. However this would deprive first generation drugmakers of the ability to recover their contribution to second-generation products. In some cases, they might decide that the expected reward was no longer sufficient to elicit R&D on the first generation drug in the first place.

Formal enforcement provisions are not the only way to assure drugmakers that rewards will be paid. Practically any demonstration of sponsors' current willingness to spend money would similarly boost credibility.\* This includes voluntarily increasing the price paid for existing drugs, increasing the quantity of existing drugs purchased,<sup>408</sup> or purchasing new drugs that appear on the market. This latter strategy could consist of frequent payouts under a large program that rewarded new drugs for multiple diseases, infrequent payouts under a narrower but longer-running program, or some combination of the two.<sup>409</sup> Because sponsor credibility increases with the number of payouts made, big budget versions of AdvancedMarkets are likely to be more cost-effective than small ones.

**Letting the Private Sector Pick Winners.** AdvancedMarkets proponents point out that sponsors need not identify promising avenues of scientific research or monitor the effectiveness with which research is pursued.<sup>410</sup> This begs the question of whether sponsors can deliver drugs more cheaply by taking on these burdens. We return to this question in Section C, below.

**Blocking Two-Stage Competition.** As explained in Section III.B.3, the prospect of post-R&D competition can create a situation in which firms refuse to race no matter how large the reward is.<sup>†</sup> AdvancedMarkets meets the threat by excluding follow-on products unless they provide a "material improvement" over earlier drugs.<sup>411</sup> Additional defenses include contract terms that stop drugmakers from offering kickbacks to LDCs that purchase subsidized drugs.<sup>412</sup>

**Political Feasibility.** AdvancedMarkets advocates sometimes argue that rich nation politicians are prepared to spend more money on solutions that involve patents than on solutions that do not. If so, it might make sense to adopt AdvancedMarkets even if its dollar-for-dollar effectiveness was low. Based on arguments presented above, AdvancedMarkets budgets might have to be twenty to thirty percent higher than competing programs for this argument to make sense.

Politics also enter the discussion in a second way. As discussed in Section III.B.2, there is some evidence that imperfect competition would allow drugmakers to capture at least part of any overpayment. If so, we might expect drugmakers to lobby for AdvancedMarkets and other proposals where substantial overpayments are likely.

### 3. Prizes.

The AdvancedMarkets proposal shares so many features with prize models that it is natural to ask whether prizes might not, after all, be a better solution. This section

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\* In theory, the best strategy would be for sponsors to set fire to a fixed amount of currency at the end of every year. Investing in current drugs is nearly as effective if we believe that sponsors will switch to improved drugs as soon as they become available.

† Industry representatives clearly understand this threat. They told AdvancedMarkets that "me-too" competition was a disincentive that needed to be suppressed. AdvancedMarkets Working Group, *Making Markets for Vaccines: A Practical Plan to Spark Innovation for Global Health*, (Center for Global Development & Global Health Policy Research Network: (Consultation Draft 2004) at p. 53

begins by asking whether Prof. Hollis' proposal for prize-based drug development – easily the most detailed current proposal – can be adapted to diseases of poverty. It then discusses several other scenarios in which prizes might improve on existing incentives.

**Hollis Proposal.** Prof. Hollis suggests replacing patents with a prize system.<sup>\*</sup> The chief benefit of his scheme is that it would eliminate the inefficient pricing associated with patents. As explained in Section IV.E, the extent to which lower prices would actually deliver benefits to patients in LDCs is unclear. The chief drawback of Hollis' suggestion is that the sponsor can no longer use market demand as a proxy for determining whether users value new drugs. Hollis argues that a public health performance measure called QALYs can fill this gap or, more precisely, that the admittedly “imperfect” QALYs<sup>413</sup> are no worse at measuring value than existing drug markets.

*QALYs.* QALYs calculate benefits to patients according to the formula “QALY = [Quality of Well Being] x [Probability of Outcome] x [Duration of Outcome].” In practice, there are two objections to this formula:

*Theoretical Objections.* Economists use many different mathematical formulae to model how users benefit from drugs. QALYs are consistent with some, but not all of these formulae. In particular, QALYs ignore the fact that benefits often change with patients' health, longevity, wealth, and risk preferences.<sup>414</sup>

*Well-Being.* Although researchers use various methods to assign “Quality of Well-Being” scores,<sup>415</sup> practical systems are limited to short questionnaires.<sup>†</sup> But questionnaires are an inherently clumsy way to measure many types of benefits, including preventive measures and “lifestyle” issues involving mental or sexual health. These shortcomings are most severe for treatments that affect “Quality of Well Being” more than other terms in the QALY formula. This category tends to include improvements to existing drugs.<sup>416</sup> Measuring these improvements is central to Hollis' scheme.

The case for QALYs is different in LDCs, where externalities often overshadow benefits to individual patients. In this case, it is tempting to reinterpret QALYs as a proxy for the value that public health authorities place on drugs. Even so, QALYs remain highly imperfect:

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<sup>\*</sup> In a more recent variant, firms could choose between patent rights and an optional, government-funded prize award. Aidan Hollis, “Optional Rewards for New Drugs in Developing Countries,” (Draft 2005)

<sup>†</sup> A typical example asks healthcare providers to assess five variables (Mobility, Pain/Discomfort, Self-Care, Anxiety/Depression and Ability to Perform Usual Activities) on a scale of one to three. The procedure results in 243 possible “Quality of Well Being” values, which are conventionally scaled to fall between 0 and 1. The authors add two additional categories – “unconscious” and “dead” – to arrive at 245 possible states. Maurice McGregor, “Cost-Utility Analysis: Use QALYs Only With Great Caution,” *Canadian Medical Association Journal* **168**:433 (Feb. 18 2003), available at [www.cmaj.ca/cgi/reprint/168/4/433.pdf](http://www.cmaj.ca/cgi/reprint/168/4/433.pdf); see also, *YourDoctorintheFamily.com*, “Ethical Implications of Cost-Effectiveness Rationing,” available at [www.yourdoctorintheFamily.com/grandtheory/section9\\_7.htm](http://www.yourdoctorintheFamily.com/grandtheory/section9_7.htm) (2004).

*Incompleteness.* Commentators emphasize that QALYs should “never be used in isolation.” Instead, policymakers must look to additional factors including “epidemiology, the health needs of the population, social and ethical factors, and local priorities.”<sup>417</sup>

*Externalities.* By design, QALYs do not capture externalities. On a per-patient basis, there is no “bonus” for creating drugs that fight epidemics.

*Data.* Current LDC disease data are too imprecise to support QALY-based prizes.<sup>418</sup> By comparison, guaranteed purchase schemes are easy to administer.

Given the small size of the sponsor community, it might be simpler for sponsors to ignore QALYs and agree on drug values directly. However, such a system would encourage drugmakers to lobby and/or offer kickbacks to sponsors. By comparison, QALYs afford less room for two-stage competition.

*Agency Problems (Sponsors).* QALY-based prizes offer multiple opportunities for sponsor discretion. These include:

*Replicability.* The replicability of QALY measurements both within and between studies is often “very poor.”<sup>419</sup> It is not clear how much replicability can be improved.

*Multiple Drugs.* Where patients receive multiple drugs, sponsors would have to devise methods for allocating benefits between drugs. These procedures can be arbitrary.

Discretion opens the door to agency problems on the sponsor side. Drugmakers will normally demand a premium to cover this risk.

**Commitment Strategies.** Like guaranteed purchase plans, prizes pose significant agency problems on the sponsor’s side. As with AdvancedMarkets, these risks can be reduced by making judicially-enforceable promises, and/or repeatedly paying awards to create a track record. However, prizes offer a third alternative: Promising to pay out a fixed sum to the best drug(s) produced each year.<sup>420</sup> Because such promises are easy to monitor, judicial enforcement is straightforward. Unless drugmakers suspect that sponsors are biased in favor of particular contestants, any remaining agency problems are likely to be minimal.

Promising to pay fixed sums is reasonable *ex ante*, since it gives competing drugmakers a strong incentive to pursue the best possible products. However, the practice may make less sense *ex post* if progress turns out to be trivial. In that case, committing to pay the entire award short-circuits the sponsor’s ability to shift funds outside the program. Offering broad prizes minimizes this danger. One obvious example would be a prize for “the best drug that treats one or more diseases of poverty” in a given year.

**Mixing Prizes and Patents.** So far we have assumed that prize winners would surrender their patent rights. In fact, sponsors frequently let prize winners keep these rights.\* While these schemes promote inefficient pricing, they also let the sponsor offer a smaller prize for any given level of R&D effort. Furthermore, requiring contestants to recover at least part of their investment through patents provides a substantial (if limited) market test of value.

Mixed patent-prize schemes also let the sponsor change normal patent rules by requiring contestants to (a) waive patent rights in certain countries, (b) create a new (and shorter) patent life than the one set by law, (c) implement price discounts for LDCs, or (d) waive their patent rights for certain uses (*e.g.* research or follow-on products). All of these options would require the sponsor to offer a larger prize. Deciding whether the first three strategies were cost-effective would be similar to the analysis presented in Section III.E, above. The fourth strategy might be justified in cases where follow-on research was expected to take place in PPPs or other non-profit environments.

**Winner-Take-Some Prizes.** Prizes are normally thought of as winner-take-all contests. This means that some runner-up technologies may be abandoned without ever reaching the market. One alternative is to split prizes among competing entrants who produce suitable drugs by a given date.<sup>421</sup> Simple calculations suggest that this “winner-take-some” scheme would elicit the same total R&D effort as conventional contests,<sup>†</sup> while allowing multiple products (here, drugs) to reach the market. In analogy with me-too drugs in rich nations, each drug would offer at least minor advantages to individual patient groups or as a steppingstone to improved products. The existence of multiple competing products would also help to constrain consumer prices.

Some drugmakers are reluctant to participate in winner-take-all drug discovery contests for neglected diseases.<sup>422</sup> Though largely forgotten, winner-take-some prizes were used extensively in early aviation contests.<sup>423</sup>

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\* The best-known example of such a mixed incentive is X-Prize for suborbital spacecraft. The winning contestant received a lump sum award but retained the right to patent and exploit its technology. The prize was not, by itself, large enough to cover R&D costs.

† Consider how three firms, each of which has the same chance of winning, decide whether to enter a winner-take-all contest. The basic calculation for each is whether the expected value of the reward exceeds its expected R&D costs:

$$(1/3 \text{ chance of winning}) \times (100\% \text{ share of expected reward}) > (\text{R\&D cost})$$

Suppose, on the other hand, that each firm is sure that it can deliver a drug by a pre-announced deadline but must share the reward. In this case, the condition for entering the race is:

$$(100\% \text{ chance of winning}) \times (1/3 \text{ share of expected reward}) > (\text{R\&D cost}).$$

At least in this simple example, the two situations are equivalent. Furthermore, the second example offers less risk. If capital markets are imperfect, reduced risk may persuade additional entrants to compete for the prize.

**Political Feasibility.** Survey data shows that the vaccine industry is skeptical of prizes.<sup>424</sup> It is reasonable to think that at least part of this attitude stems from lack of familiarity. Experiences at DARPA<sup>425</sup> and NASA<sup>426</sup> suggest that business can and does respond to well-designed prizes.

## 4. Grants.

In theory, end-to-end rewards can elicit discovery at all phases of the drug discovery pipeline. However, end-to-end contests encourage competing groups to hoard information. Anecdotal evidence suggests that commercial secrecy is a significant obstacle for neglected disease research.<sup>427</sup> For this reason, there is widespread agreement that early-stage research should be supported by “push” mechanisms. As we have seen, the ability to elicit and share widely scattered information continues to be important through target validation and – in some cases – lead compound identification. [Section III.C.3] For this reason, sponsors may need to support end-to-end systems with grants until competing companies start to develop specific compounds.

## B. Pay-As-You-Go Solutions.

Pay-as-you-go solutions force sponsors to design incentives for each step in the drug discovery pipeline. Because rewards are paid out repeatedly in small increments, agency problems on the sponsor side are automatically smaller than they would be for end-to-end systems. Unlike end-to-end systems, pay-as-you-go schemes can also take advantage of incentives (*e.g.* competitive bidding) that feature strong cost containment. This section examines the incentive systems that pay-as-you-go programs are likely to adopt. The potential weaknesses of pay-as-you-go solutions are deferred to Section IV.C, below.

### 1. Prizes.

Pay-as-you-go prizes provide rewards for intermediate successes along the drug discovery pipeline. Winner-take-all prizes offer rewards to the first researcher to complete a given research task. “Best entry” prizes reward whichever entry produces the most promising result within a fixed period.<sup>428</sup>

**When Prizes Are Appropriate.** Prizes are routinely used to solve industrial chemistry problems. [See, Section III.C.6] Most of these prizes are offered by a company called InnoCentive. InnoCentive claims to produce viable solutions for about forty percent of all challenges.\* Furthermore, most of its prizes are modest (\$5,000 to \$100,000<sup>429</sup>), confirming speculation<sup>430</sup> that prizes for *ideas* (as opposed to working artifacts) can be relatively small. Finally, InnoCentive usually retains broad discretion in

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\*Most challenges involve problems that sponsor have already tried and failed to solve on their own.

deciding when (and if) to pay for solutions. This suggests that agency problems are manageable.

It is natural to ask whether prizes might work equally well for drug discovery tasks that do not involve chemistry. In general, prizes make sense for R&D steps where (a) eliciting information is important, and (b) the danger of overpayment is small. We have seen that both conditions tend to hold for many early phase drug discovery projects. Examples include finding targets, optimizing targets, finding lead compounds, and optimizing compounds.

Alternatively, prizes also make sense where there is broad consensus about the value of achieving particular goals. In neglected disease research, prizes for protein-based pneumococcal vaccines and new animal models for drugs and vaccines<sup>431</sup> probably fall in this category.

**Best Entry Prizes.** As explained in Section IV.A.3, best entry prizes are a powerful method for minimizing agency problems on the sponsor side. The principal drawback is that sponsors must still pay if R&D is not productive. This risk is probably acceptable when the prize seeks to elicit results similar to those that are routinely achieved in rich nation diseases. This suggests that, for example, best entry prizes are an appropriate method for finding targets and compounds are plentiful for rich nation diseases. The case is more doubtful where sponsors seek to develop products or research tools that have no existing precedent. In this case, the underlying science may be difficult so that “best-entry prizes” are inappropriate.

Finally, Prof. Kremer has argued that best-entry prizes may encourage firms to focus on getting results within the prize period.<sup>432</sup> Making prize periods longer and/or offering successive prizes for similar research can alleviate this problem.

**Political Feasibility.** Prof. Kremer argues that best entry contests are politically unattractive because the winning idea may never pay off. However, this effect is offset by the fact that best entry prizes tend to be smaller and less visible than end-to-end prizes. The net effect on political feasibility is ambiguous.

**Applications.** Prizes provide a powerful method for eliciting information while avoiding the inefficient pricing associated with patents. Cost-containment is relatively unimportant for early stage prizes, where R&D costs are small in any case.

## 2. Contract Research.

We have seen that commercial drugmakers purchase contract research throughout the drug discovery R&D pipeline. Encouraging vendors to compete for contracts is a powerful cost containment strategy.

**Contract R&D.** We have argued that contract research is most viable when sponsors can monitor and enforce agreements. In general, this task becomes easier for late stage discovery, where tests tend to be more routinized and less creative. Section III confirms that drugmakers often outsource late-stage drug discovery from pre-clinical trials onward. High throughput screening – which is literally performed by robots – offers another promising venue for contract research.

Sponsors also use contracts to fund the development of manufacturing processes. This usually involves purchase contracts in which sponsors promise to buy a fixed quantity of drugs if the manufacturer finds a way to make them. Examples include polio<sup>433</sup> and, more recently, bird flu vaccines<sup>434</sup>. The main advantage of purchase contracts is that the sponsor pays nothing if the manufacturer fails to develop a suitable process. This is a sensible rule, since the manufacturer is almost always better able to gauge the chances of success than the sponsor. Conversely, the manufacturer bears no risk if the vaccine turns out to be worthless. This is reasonable if manufacturers have no special knowledge about which vaccines are likely to succeed.

**Kucinich Proposal.** US Congressman Dennis Kucinich has suggested extending the contract R&D model by paying ten publicly-funded research corporations \$25 billion to develop new drugs. The main advantage of Kucinich’s proposal is that it would eliminate the patent monopoly for new drugs, and therefore cut prices *ex post*.<sup>435</sup> The main difficulty would be agency problems on the researcher side:

*Monitoring Researchers* Kucinich’s proposal includes early phase discovery where contract research presents significant agency problems. In principle, Kucinich’s corporations could avoid this problem by outsourcing early phase work through prizes and other non-contract incentives.

*Enforcing Productive Research.* Congressional oversight is cumbersome and a poor guarantor of efficiency. A more effective mechanism might be for government to replicate commercial incentives by threatening to de-fund inefficient corporations. The success of this strategy would depend on whether government was willing to de-fund failure as ruthlessly as private sector shareholders do. Kucinich’s corporations are likely to be inefficient if – as this paper has consistently assumed – government spending patterns are hard to change.

**Applications.** Contract research makes sense where agency problems on the research side are small. High throughput screening, pre-clinical tests, and clinical trials all fit this description. Contract research is a powerful tool for containing costs.

### 3. Open Source.

Historically, corporations have used highly disciplined, hierarchical teams to design complex inventions. Examples include aircraft, rockets, microprocessors, software, and pharmaceuticals. During the 1990s, however, the open source movement

showed that at least one of these products (software) could be organized in a much looser and more decentralized way. It is reasonable to think that similar methods can be used to organize at least some phases of drug discovery, although, this has yet to be demonstrated.\* This section reviews current proposals.

**Computational Drug Discovery.** Maurer *et al.*<sup>436</sup> have pointed out that searching for protein targets and lead compounds in a large DNA database is analogous to finding and fixing bugs in a large operating system. In principle, open source methods offer three advantages:

*Scientific Efficiency.* Open source proponents claim that decentralized “many eyeballs” searches are a powerful method for sifting small features from an ocean of code. Furthermore, competing academic and commercial laboratories tend to splinter information across multiple teams. An open source collaboration would cut across these divisions by encouraging researchers to work together on a community-wide basis.

*Volunteers.* Today, computational biologists have no effective vehicle for donating their skills to neglected disease research. An open source initiative would fill this gap. Volunteer labor is likely to be particularly valuable in the under-funded world of neglected disease research.

*Economics.* Open source discoveries would either not be patented, or else patented subject to licenses that gave public sponsors and LDCs broad research and manufacturing rights. Section IV.D.4 argues that limiting patents can cut R&D and manufacturing costs. Furthermore, this is true even if open source turns out to be scientifically inefficient. As Prof. Farlow has emphasized, open source biology only has to work “‘sufficiently’ well”<sup>437</sup> to overcome the drawbacks associated with patents.

*Industry Collaboration.* Because neglected diseases have negligible commercial value, drugmakers would lose nothing by sharing proprietary data.<sup>†</sup> However, an open source collaboration must still assure donors that shared data would not be diverted back into R&D for rich nation diseases. This can be done in several ways:

*Access Agreements.* The simplest way to protect data against unauthorized disclosure is by contract. Monsanto and Syngenta already share data on this basis.<sup>438</sup>

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\*Current references to “open source biology” are almost always a misnomer, referring either (a) to software, or (b) to collaborations that collect and publish information without claiming patent rights. *See, e.g.,* K. Cukier, “Community Property,” *Acumen* 1:54 (2003); D. Hamilton, “Open to All,” *Wall Street Journal* (May 19, 2003). The former are indistinguishable from other forms of open source software. The latter are indistinguishable from traditional academic science.

<sup>†</sup> This assumption will become less realistic if growing budgets for neglected disease research start to bid up the price of data and research tools.

*Oracles.* Databases derive value from assembling massive amounts of information but lose little if one or two isolated “hits” are disclosed.<sup>439</sup> For this reason, commercial vendors often protect data by asking customers to submit queries. Because customers never see the actual database, the chances of misappropriation are small. An open source drug collaboration could adopt a similar strategy by asking commercial vendors to serve as “oracles.” In this scheme, oracles would search sensitive in-house databases in response to questions posed by the collaboration. Oracles could also warn volunteers against pursuing ideas that the company had previously tried and discarded.<sup>440</sup>

*Compound Libraries.* Compound libraries are conceptually similar to databases.\* Anecdotal evidence suggests that companies may be willing to donate high throughput screening services in much the same way that they currently share data.<sup>441</sup>

For now, open source computational drug discovery is plausible but not proven. The principal uncertainties are (a) whether biologists would volunteer for the project in significant numbers, and (b) whether *in silico* methods (perhaps augmented by modest experiment budgets) are sufficiently powerful to discover useful targets and compounds. The only way to resolve these uncertainties is to try the experiment. Duke University will hold a three-day workshop to explore design issues in May, 2005.

**Open Source Chemistry.** Maurer *et al.*<sup>442</sup> have noted that academic researchers may be able to divert (“scrounge”) chemistry and biology resources from existing grant budgets. In practice, even modest experiments would make computational drug discovery much more productive. Benkler<sup>443</sup> has further suggested that data from experiments could be traded under open source licenses. Because scrounged resources are costless to researchers (if not grant agencies), incentives for researchers to trade and share results would be similar to those found in open source software collaborations. Even though grant agencies have an obvious incentive to limit scrounging, such resources could still be significant by the standards of neglected disease research.

In principle, governments and private sector firms could also fund researchers to perform open source chemistry experiments explicitly. Because these models introduce a significant risk that researchers may pocket or divert funds, they are fundamentally different from the basic open source paradigm introduced in Section III.B.6. We discuss these models in Section IV.B.4, below.

**Commercial Analogs.** Open source proponents frequently assume that open source methods are incompatible with commercial discovery. This argument is incorrect to the extent that open source volunteers are motivated by incentives like education, benefits to reputation, and the opportunity to advertise skills to employers. Open source methods are also consistent with commercial incentives. Microsoft’s Shared Source

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\* Like a database, compound libraries are expensive to make but, once created, can be consulted at relatively low marginal cost.

Initiative<sup>444</sup> is an interesting experiment in merging intellectual property with open source incentives.

Open source may be less compatible where volunteers are motivated by ideologies that are hostile to commercialization. Even here, however, volunteers could decide on pragmatic grounds that commercial development was the best way to help LDCs.

**Off-Label Testing.** Prof. von Hippel has pointed out that open source collaborations are a natural way to collect and analyze patient data in order to demonstrate new (“off-label”) uses for existing drugs.<sup>445</sup> In the context of neglected disease research, off-label studies are frequently sued to extend existing drugs to new geographic areas and indications, obtain approval for drugs that are already in informal use, and test new doses or formulations.<sup>446</sup> Significantly, contract research sometimes encourages researchers to falsify data so that they can collect payment for non-existent work.<sup>447</sup> This type of agency problem would be negligible for open source collaborations staffed by volunteers.

Interestingly, neglected disease research already offers a partial analog to von Hippel’s proposal. Oxford University’s gMap project routinely collects and performs genetic testing on patient specimens from around the world. The resulting data are used to support (a) a large Oxford epidemiological study of neglected diseases, and (b) individual collaborations with approximately two-dozen LDC scientists.<sup>448</sup> Neither of these activities qualifies “open source” since individual projects are usually limited to a handful of participants and center on basic research rather than drug development *per se*. Nevertheless, gMap’s architecture is intriguingly similar to the patient networks that von Hippel envisages.

von Hippel’s suggestion is special: It works because the drugs and doctors needed to support Phase IV trials have already been paid for by the healthcare system. The case is very different for Phase I through III trials, where the cost of providing drugs and caregivers is prohibitively expensive. For this reason, Phase I through III open source collaborations will almost certainly require drugmaker support.\*

**Applications.** In theory, open source methods provide an attractive mechanism for (a) conducting computational searches for targets and lead compounds, (b) performing modest chemistry searches to validate and extend computational discoveries, and (c) extending previously approved drugs to new “off-label” applications. Modest experiments would go some distance to determining the value of these methods.

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\*There are at least three reasons why drugmakers might fund open source methods. First, volunteer labor is attractive. Second, as previously noted, open source collaboration poses less danger of scientific fraud. Finally, drugmakers might decide that open source’s transparency would make results more persuasive to FDA.

## 4. Grants.

Government agencies usually award grants for basic research but rely on patent incentives to turn good ideas into drug targets. This option does not exist for neglected disease research, where patent incentives are minimal. It is therefore worth asking whether the traditional grant model can be extended to early phase drug discovery. More ambitiously, some commentators suggest that government should fund “Open Source Chemistry” collaborations to find and optimize lead compounds. These proposals are similar to modern “Big Science” grants. We consider each of these strategies below.

**Traditional Grants.** The social challenges facing early-stage drug research center on (a) eliciting widely-scattered information, and (b) controlling agency problems on the researcher side. As noted in Section III.C.1, these are the same challenges found in basic research. The main uncertainty is whether academic scientists would be interested in doing applied research.<sup>449</sup> If not, scientists might waste or divert resources even if they were cut off from future grants as a result. Theory cannot resolve this question. The only way for foundations to find out whether grants are effective is to do the experiment.\*

**Big Science Grants.** Commentators sometimes argue that government agencies should support “Open Source Chemistry” communities by subsidizing experiments so that they become as costless as writing code. The main obstacle to such schemes is that researchers might pocket or divert the subsidies. Monitoring multi-year experiments involving hundreds of researchers is a daunting prospect.

Since the 1940s, grant agencies have faced similar problems involving Big Science experiments (*e.g.* large atom smashers) in the physical sciences. The solution has been to let scientists create large, self-governing groups. The benefit of this system is that agencies can delegate monitoring to a handful of leaders. Because the leaders are accountable, the system seems to be reasonably efficient. In 2002, The Alliance for Cell Signaling (“AfCS”) extended this Big Science model into the realm of “Big Biology.” AfCS currently relies on eight laboratories and forty full-time staff project to map the massively complex chemical signals found in human cells. An additional 1,000 experts participate and receive funding intermittently.<sup>450</sup>

*Open Source Chemistry.* In principle, an Open Source Chemistry collaboration could work the same way. In this model, volunteers interested in optimizing a particular lead compound would form a group and apply for grants. Once work began, principal investigators would monitor progress and terminate payments to unproductive workers. Results would be shared within the group so that members could follow up on whatever results seemed most promising.<sup>†</sup>

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\* As explained below, the Bush Administration has proposed grants for translational research as late as preclinical to human trials.

† The role of contracts in such a scheme is obscure. The main danger seems to be that corporations might monitor the site, identify promising discoveries, and then rush to patent trivial improvements. In principle, Big Science collaborations can block such a result by requiring users who access the site to agree to an

*Global HIV Vaccine Enterprise.* President Bush proposed an even broader Big Biology grant when he called for a “Global HIV Vaccine Enterprise” at the G-8 Summit in June 2004.<sup>451</sup> Though lacking details, the proposed enterprise would be “analogous to the successful alliance and strategic plan that characterized the approach to the human genome project.” The project would include (a) “development centers” to create reagents and perform preclinical experiments, (b) “vaccine science consortia” for translating preclinical leads toward clinical development, and (c) more clinical trials capacity in LDCs.<sup>452</sup> Both the “development centers” and the “vaccine consortia” would apparently be funded through Big Science grants.\*

Interestingly, proponents seem to think that the centers and consortia would need relatively little input from the broader scientific community.<sup>453</sup> This suggests that the chief advantage of grants – eliciting information – is largely superfluous and that other institutions (*e.g.* contract research) might be preferable on cost-containment grounds. It is similarly unclear why “consortia” would be preferable to a single institution. The answer may be that consortia would encourage academic and commercial scientists to talk to one another. This would facilitate the task of “translating” preclinical leads into products that companies can test in humans.

**Applications.** It is reasonable to think that traditional grants can be extended beyond basic research to include finding and validating targets. Big Science grants may be a viable method for finding and optimizing lead compounds.

## 5. Harry Fox Licenses.

US law requires music publishers in some markets to exchange songs at a legislated price, but then permits pairs of publishers to opt out by negotiating “Harry Fox” licenses in which the parties agree on a different price.<sup>454</sup> Interestingly, these prices are reasonable because a publisher who demands an exorbitant price for its own music must pay the same prices when it purchases music from others. Lewis & Reichman argue that the Harry Fox model should be extended to “small scale innovation” generally.<sup>455</sup>

The conditions needed for Harry Fox licenses – low value, fungible information – are relatively special.<sup>†</sup> In the context of drug discovery, lead compound searches probably come closest to meeting these criteria. As explained in Section III.C.3, individual compounds in chemical libraries typically have only a one in 100,000 chance of becoming “leads.” This observation suggests that Congress could use Harry Fox

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open source license. The problem with this suggestion is that some improvements might never be created without patent incentives. In this case, contract restrictions would impoverish society. A simpler and more elegant solution would be to embargo access for a reasonable length of time so that academic scientists got “first crack” at any extensions.

\* Government bodies already use grants and contracts to build clinical trials capacity in LDCs. [See Section III.C, *supra*]. The Bush proposal would presumably expand these existing institutions.

† The Harry Fox conditions automatically exclude agency problems and/or problems in eliciting information. This leaves efficient pricing as the principal challenge.

legislation to force pharmaceutical companies to sell access to each others' chemical libraries.

Such legislation is politically unlikely. A more promising alternative might be for Congress to set a default price at which drugmakers could trade compounds based on indigenous knowledge. In analogy with the music industry, drugmakers would then negotiate bilateral Harry Fox agreements. At this point, companies would be able to purchase each others' data without further negotiation. LDC governments would receive a fixed fraction of each transaction.\*

## 6. A Benchmark Strategy

The preceding discussion provides a detailed comparison of possible incentives against the social challenges identified in Section III.C. Table 5 concludes this discussion by summarizing a logical sequence of incentives for a pay-as-you-go drug development program.

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\*It is natural to ask why LDC governments cannot not sign Harry Fox agreements directly. The reason is that Lewis & Reichman's mechanism only works where each party simultaneously buys and sells data. Although LDCs produce traditional knowledge, they seldom purchase it. The flaw is not fatal. Music publishers who negotiate Harry Fox licenses routinely share revenues with songwriter/clients. Lydia Pallas Loren, "Untangling The Web of Music Copyrights," 53 Case Western Reserve Law Review 673 (2003).

**Table 5:  
Non-Patent  
Drug Discovery Incentives.**

Discovery Phase	Main Social Challenges	Preferred Institutions
1. Basic Research	Agency problems on the researcher side; eliciting information	Grants
2. Target Identification and Optimization	Agency problems on the researcher side; eliciting information	Best entry prizes. Open source.
3A. Lead Compound Discovery: High Throughput Screening.	Minimal (Risks are Entirely Scientific)	Contract Research. Best entry prizes.
3B. Lead Compound Discovery: High Throughput Screening, Computational Methods, Combinatorial Chemistry	Agency Problems on the Researcher Side	Contract Research. Best entry prizes.
3C. Lead Compound Discovery: Traditional Knowledge/Local Plants	Eliciting Information	Best entry prizes. Harry Fox Licenses
4. Lead Compound Optimization	Modest agency problems on the researcher side.	“Big science” grants. Contract R&D.
5. Pre-Clinical R&D	Cost-containment. Agency problems on the researcher side.	Contract R&D
6. Process Development	Cost-containment. Eliciting information	Contract R&D; best entry prizes
7. Phase I Trials	Cost containment. Agency problems on the researcher side.	Contract R&D; use of competitive bidding and repeat contracts to enforce low prices; in-house management of all FDA contacts.
8. Phase II Trials	Cost containment. Agency problems on the researcher side.	Contract R&D; use of competitive bidding and repeat contracts to enforce low prices; in-house management of all FDA contacts.

9. Phase I Trials	Cost containment. Agency problems on the researcher side.	Contract R&D; use of competitive bidding and repeat contracts to enforce low prices; in-house management of all FDA contacts.
10. FDA Approvals	Cost containment. Agency problems on the researcher side.	Contract R&D; in-house management of all FDA contacts.
11. Manufacturing	Cost containment. Agency problems on the manufacturer side	Contract production; use of competitive bidding and repeat contracts to enforce low prices.
12. Phase IV and Off-Label Trials	Agency problems on the manufacturer side.	Contract R&D; open source collaborations.
13. Marketing and Distribution	None. PPPs and public health agencies have better information about distribution than drugmakers.	Existing private markets and public distribution channels.

## C. Private-Public Partnerships.

Since the late 1990s, sponsors have devoted large sums to giving Private Public Partnerships (“PPPs”) the R&D management skills normally associated with commercial drugmakers. This section evaluates criticisms that PPP teams are inherently less capable than their private sector counterparts. It also examines current strategies for putting PPP expertise to use.

### 1. Can PPPs Pick Winners?

Many people believe that private sector firms are invariably more efficient than government or non-profits. The most commonly cited example is probably defense procurement.\* Even here, however, the actual evidence tends to be thin.† Over the past quarter century, US Army’s Medical Research Institute of Infectious Diseases has developed vaccines for Argentine hemorrhagic fever, Venezuelan equine encephalitis Rift Valley fever, tularemia, infant botulism, and other diseases.<sup>456</sup> A systematic comparison of these programs against private sector initiatives would go some distance toward deciding the relative efficiency of government and private sector vaccine programs. More fundamentally, this paper has emphasized that institutional inefficiency is rooted in incentives. In order to be instructive, we would have to ask *why* Pentagon officials cannot contain costs and whether these same incentives are somehow generic to public/non-profit organizations as a whole. Until this is done, the usefulness of the Pentagon analogy is likely to remain obscure. In what follows, we explore the much narrower question of why PPPs might be inefficient and what can be done to mitigate this risk.

Since PPPs frequently hire former private sector executives and government regulators, basic competence is presumably not an issue.<sup>457</sup> Instead, any shortfall must reflect different incentives. In the private sector, the incentive to perform efficiently comes from profit-maximizing shareholders who ruthlessly de-fund companies that fail to find drugs cost-effectively. In the non-profit world, foundations play this role. This section asks whether foundations’ ability to detect and de-fund failure makes PPPs less efficient than they otherwise would be.

**Detecting Failure.** Organizations cannot conduct R&D efficiently if researchers are able to prolong scientifically weak projects for dysfunctional reasons such as prestige, bureaucratic power, and subjective bias.<sup>458</sup> In practice, managers’ ability to overrule

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\* The alleged inefficiency of Pentagon procurement should not be taken on faith. Economists who study military procurement suggest that firms competing for sole source manufacturing contracts see the prospect of above-normal profits as a *de facto* prize. Rogerson, W. (1994), “Economic incentives and the defense procurement process,” *J. Economic Perspectives*, 8:65-90. In this view, cost-overruns could reflect a mechanism (prizes) that tends to encourage new ideas at the expense of strict cost-containment.

† AdvancedMarkets proponents usually point to the “cautionary tale” of USAID’s Malaria Vaccine Program in which, *inter alia*, the project manager had an affair with one of her grant recipients. See, e.g., Kremer & Glennerster, *Strong Medicine* (2005) at pp. 47-49 Presumably, the story is *not* meant to imply that USAID as a whole is corrupt – or that similar scandals do not occur in private companies.

researchers depends on their ability to independently judge the value of R&D programs. There are several reasons to think that such monitoring is feasible. First, the goal of most drug development is to generate data for the FDA. Companies can judge this information just as well as regulators. Second, modern drug management offers various objective methods for deciding whether portfolio milestones are being met, portfolios are being pruned, and R&D priorities are being adjusted to reflect new data.<sup>459</sup> This makes it hard for researchers to hide evidence of failure. Finally, private firms routinely assign outside employees to take a second look at existing projects.<sup>460</sup> The existence of these audits suggests that agency problems exist but are also manageable.

Based on this evidence, it is reasonable to think that foundations can detect PPPs that retain drug candidates past the point where they ought to be discarded. Indeed, PPPs often point to discarded candidates as a sign of professionalism. That said, PPPs may view the matter differently when a drug candidate represents a large fraction of their remaining portfolio. The best way for foundations to avoid this risk is to avoid funding PPPs with very small portfolios.

**Willingness to De-Fund Failure.** Ideally, foundations should be prepared to de-fund PPPs as quickly as shareholders de-fund private drugmakers.\* This philosophy is very different from conventional grant models, which tend to review programs infrequently. While there is no objective reason to think that foundations cannot emulate shareholders, institutional habits may stand in the way. Politics will also make the task harder. For example, large foundations often argue that their spending is leveraged when small sponsors make matching grants. This encourages PPPs to make the absurd claim that “success in mobilizing sufficient funds” is an accomplishment in its own right.<sup>461</sup> Conversely, small sponsors sometimes try to increase their visibility by earmarking donations to a specific drug candidate instead of the PPP’s entire portfolio.<sup>462</sup> This practice creates obvious incentives for PPPs to retain drug candidates past the point of rationality.

**Ability to De-Fund Failure** Willingness is just part of the equation. Foundations must also structure grants so that the threat to de-fund is credible. Current problems include:

*Mission Bundling.* Sponsors find it harder to de-fund organizations that bundle poor portfolio management with other missions. For this reason, sponsors should refuse to fund PPPs that combine management with unrelated activities such as education, advocacy, and, perhaps, access.<sup>†</sup>

*Entity Bundling.* Similar problems occur when the PPP is funded as part of a larger entity. Roughly half of all PPPs fall into this category.<sup>463</sup>

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\* This is not to say that private shareholders find it easy to de-fund companies. Given that most drug candidates fail in the best of cases, it is hard to distinguish bad luck from systematic incompetence. Foundations should expect to emulate the performance of private shareholders, not exceed it.

† Access programs define a borderline mission. Experience in rich nations suggests that it may be efficient to have the same company conduct both drug development and marketing. This observation does not prove that the two activities have synergies for LDCs.

*Competing PPPs.* Sponsors find it harder to de-fund organizations which – however inefficient – have the only existing R&D programs for a particular disease. PPPs should be sufficiently numerous so that sponsors can credibly threaten to de-fund entities that fail to perform.

Based on the foregoing factors, it is reasonable to think that contemporary PPPs may be harder to de-fund than commercial drugmakers. This is a distinct, but also remediable, handicap. At the end of the day, foundations’ decision to adopt Virtual Pharma models could turn on their willingness to emulate private sector shareholders.

## 2. Strategies

Sponsors face a fundamental choice whether to pursue drug development through guaranteed price incentives (AdvancedMarkets) or direct development by non-profit entities (Virtual Pharma). This section focuses on how PPPs can support either scenario.

**Virtual Pharma.** Critics of Virtual Pharma solutions argue that “[i]ndividual scientists and firms working on the problem are best placed to judge scientific prospects” and have “a vested interest in misleading sponsors.”<sup>464</sup> However, Section III.C has emphasized that commercial drugmakers routinely face similar problems when outsourcing R&D. In response, drugmakers have devised various strategies including aggressive monitoring and negotiation, competitive bidding, and the prospect of repeat business. Significantly, the last factor depends on purchasing power. This suggests that Virtual Pharmas are likely to become more cost-effective as budgets grow. Even if PPP budgets do not increase, shrewd purchasing strategies can also make PPPs more efficient. Possibilities include:

*Purchasing Tactics.* PPPs should bargain hard, monitor work closely, employ competitive bidding, and use the prospect of repeat business as a performance incentive. Recent PPP/drugmaker agreements that embrace multiple compounds are a first step in this direction.<sup>465</sup>

*Consolidating PPPs.* The simplest way to increase the average PPP’s purchasing power is to reduce the total number of PPPs. Given that there are currently more PPPs than large drugmakers, consolidation appears inevitable.<sup>466</sup> As previously noted, consolidation should not proceed to the point where foundations are afraid to de-fund individual entities.

*Partnering With Small Firms.* As noted in Section III.C.6, small biotech companies often purchase contract research from other small firms so that their projects will receive more attention. Some PPPs follow a similar strategy by providing up to one-half of their private partner’s income.<sup>467</sup> Such strategies will normally be less attractive where large firms possess unique assets, economies of scale, or other advantages.

*Pooling Purchases.* Many observers argue that existing PPPs should share more platforms, clinical trials infrastructure, and manufacturing capacity.<sup>468</sup> One natural way to generalize this suggestion would be for groups of PPPs to award “preferred vendor” status to contract R&D companies that consistently provide value-for-money.<sup>469</sup>

*Stable Funding.* Most PPPs rely on piecemeal funding from a large and shifting group of donors.<sup>470</sup> Strong, stable funding would encourage industry to take PPP partners more seriously.<sup>471</sup>

None of these solutions is perfect. Agency problems will remain, just as they do in the private sector. The question is not whether Virtual Pharma is imperfect, but only whether it is *less* imperfect than every other alternative.

**Strategic Investing.** Advocates of strategic investing argue that targeted subsidies can persuade companies to undertake marginal projects in cases where low expected profits and/or risk are otherwise prohibitive. The danger for such strategies is crowding out, *i.e.* that public dollars will replace private investment with no net increase in investment. For now, there appears to be little information about how large crowding out effects actually are. Intriguingly, Robert Ridley argues (a) that total private sector R&D activity has grown since the late 1990s, and (b) that PPP subsidies have produced most of this additional activity.<sup>472</sup> A more systematic analysis is urgently needed to confirm Ridley’s conclusion and to determine whether PPP subsidies are an efficient method for attracting matching investments from commercial drugmakers.

*False Economies.* Strategic investing makes sense if, and only if, it generates net additional resources for sponsors fighting neglected diseases. Unfortunately, most PPPs take a more parochial view, arguing only that partnerships generate new assets for their own individual programs. This analysis is incomplete unless one asks how private partners expect to be repaid. In the simple case where the partner expects to recover all of its costs through sales to governments and non-profit entities, sponsors receive no additional assets. Sponsors can, however, lose assets. The reason is that private partners have a strong incentive to demand more subsidies than are actually needed to elicit investment. Given PPPs’ limited ability to detect such posturing, some overpayment is inevitable. *Ceteris paribus*, sponsors will normally find it cheaper to fund PPPs directly instead of purchasing patented drugs after-the-fact.

The calculation is more complicated where the private partner expects to earn at least part of its income from sales to middle- and upper-class patients in LDCs or the developed world. In this case, the sponsors can receive additional net new assets for fighting disease. Nevertheless, such strategies may not be viable if they threaten access for the poor.

Finally, commentators frequently urge PPPs to choose between Virtual Pharma and Strategic Investing models based on such factors as (a) whether a Strategic Investing model would save the PPP from having to hire additional staff<sup>473</sup> or enlarge its

portfolio,<sup>474</sup> or (b) whether the private sector has existing R&D programs in-place.<sup>475</sup> Such analyses ignore the fact that new staff and/or new programs may be the most efficient solution. Sponsors should look for strategies that promise the best return even if that means changing existing ways of doing business.

**Reaching a Decision.** This paper has argued that the main criterion for choosing between Virtual Pharma and AdvancedMarkets is (or should be) price. Based on the evidence cited above, expected overpayments under an AdvancedMarkets model could easily reach twenty to thirty percent. On the other hand, sketchy evidence from the chemical industry suggests that large drugmakers' purchasing power can potentially make outsourcing five to twenty percent more cost-effective. On this admittedly limited evidence, Virtual Pharma could be the most efficient solution.

For now, the largest uncertainty associated with Virtual Pharma strategies is whether PPPs can manage portfolios as efficiently as their private sector counterparts do. Here, the main factor is whether foundations are willing to de-fund failed PPPs as readily as private sector shareholders would. Ironically, foundations may be the only ones who can answer to this question. This self-assessment could be the key to deciding between Virtual Pharma and AdvancedMarkets.

## D. Supporting Institutions

### 1. Universities and Governments.

Many PPP compounds are licensed from academic institutions.<sup>476</sup> Despite this, most universities lack clear licensing policies for neglected diseases.<sup>477</sup> Yale University's recent decision to license an athlete's foot compound to drugmakers while reserving the right to license the same compound at much lower (or even zero) royalties for Chagas disease is one promising model.<sup>478</sup> The simplest option would be for university licensing offices to grant the public a royalty-free license to use their patent portfolios to develop and use drugs for neglected diseases in any LDC. This option is also affordable, since licensing offices are not likely to earn substantial profits from LDC markets in any case. As noted below, placing multiple compounds in the public domain would reduce R&D costs for neglected disease throughout the drug development pipeline.

### 2. R&D Treaty

Hubbard and Love<sup>479</sup> have suggested an international R&D treaty under which each signatory would promise to devote a minimum fraction of its GDP to drug research. Within individual countries, the expenditures could be made directly by governments, posted as R&D prizes, or contributed under an "intermediator" system in which individuals or employers were required to invest a specified fraction of their income in

one or more R&D companies. This paper has already discussed the first two options at length. We focus on the “intermediator” proposal in what follows.

On its face, Hubbard & Love’s intermediary proposal appears similar to US “Individual Retirement Accounts” and other government-mandated savings plans. However, the analogy is incomplete. Because savings accounts are “rival” (*i.e.*, can only be enjoyed by one person at a time), every employee (including the pension fund manager) has a direct stake in making high-quality decisions. The case is fundamentally different for information goods like drugs. Unlike pension fund proceeds, knowledge of new drug compounds can (once discovered) be shared with an infinite number of users. This means that success by *any* intermediary would benefit *all* consumers – including those who invest foolishly. Supposing for argument’s sake that ten million businesses made investment decisions, the incentive to make correct decisions would be negligible. In principle, legislatures could fix the problem by passing laws to make new drug knowledge “rival.” But this is precisely what the patent system already does – and the result that Hubbard & Love wish to avoid.

The same logic also applies at the international level. Realizing that they can gain little from even the wisest investments, small countries will normally spend their investment in ways that support local R&D providers (however inefficient) instead of sending funds abroad. The situation is still worse if small countries are able to divert funds to other uses. Preventing this result would require (a) a massive accounting system for tracking worldwide R&D spending, and (b) quick and effective procedures to punish cheaters. Neither condition is likely to hold in practice.

### 3. Regulatory Bodies.

Today’s neglected disease R&D programs typically seek FDA approval. However, most sponsors depend on the WHO – not FDA – to “prequalify” drugs.<sup>480</sup> This suggests that WHO has the power to transfer FDA’s role to other regulators. A WHO initiative to create and empower local or regional regulators would cut R&D costs in three respects:

*Increasing LDC Trials Capacity.* In theory, trials can be run under FDA guidelines anywhere. In practice, many drugmakers are reluctant to run trials in LDCs without local regulatory authorities.<sup>481</sup> Removing this bottleneck would increase the number of firms willing to perform trials in LDCs and, through competition, reduce costs.

*Streamlining Regulation.* Section III.C has emphasized that FDA requirements drive a large fraction of drugmaker testing. Not surprisingly, many commentators complain that FDA procedures inflate R&D costs.<sup>482</sup> Streamlined procedures would be a powerful corrective.

*Eliminating Inappropriate Standards.* FDA rules were designed for rich nations where infection rates (and associated externalities) are low. It is therefore

reasonable to think that LDCs should adopt different rules that, *inter alia*, place greater emphasis on the need to deliver new drugs.<sup>483</sup> European proposals for a special approval status for drugs marketed outside Europe are a first step in this direction.<sup>484</sup>

Creating indigenous regulation by LDCs is often seen as a symbolic issue. It may also be a powerful strategy for cutting R&D costs.

#### 4. The Public Domain.

Several commentators have noted that PPPs need more upstream research to keep their development pipelines full. While this is a scientific observation, upstream research may make even more sense on economic grounds. We examine these arguments separately for Virtual Pharma and AdvancedMarkets scenarios.

*Virtual Pharma.* Since patents play little or no role in Virtual Pharma development, a strong public domain radically simplifies development. It also makes it less costly:

*Un-Patented Compounds.* We have argued that competition in general and competitive bidding in particular are powerful mechanisms for containing cost. Based on the evidence presented in Section III.C, it is reasonable to think that outsourcing will be markedly more effective if drug candidates remain unpatented.

*Patented Compounds.* In theory, PPPs should never agree to pay more for a patented compound than it would cost to bring a new public domain chemical (or a new idea for an old, off-patent drug) to the same point. In practice, the existence of public domain alternatives means that PPPs can threaten to “walk away” when bargaining with recalcitrant patent owners. PPPs have relatively little bargaining leverage in today’s world, where drug development programs for neglected diseases rarely face competing compounds.<sup>485</sup>

Based on the foregoing arguments, it is reasonable to think that a focused initiative designed to expand upstream, public domain research would produce significant cost savings for PPPs throughout the drug development pipeline.

*AdvancedMarkets.* The case for a strong public domain is less clear for AdvancedMarkets. Nevertheless, there are at least two reasons to think that a strong public domain could make AdvancedMarkets incentives more effective:

*Drugmaker Costs.* Incentives are more powerful when drugmakers face low R&D costs. During the 1990s, large drugmakers decided that it was cheaper to discover “single nucleotide polymorphisms” or “SNPs” themselves than to let biotechnology companies do the work and collect patent royalties.<sup>486</sup> Drugmakers ultimately paid academic scientists more than \$60 million to find and donate this

information to the public so that one could patent it. Putting targets and potential compounds in the public domain might similarly contain costs for companies participating in an AdvancedMarkets program.

*Patent Thickets.* Many scholars claim that proliferating intellectual property rights can create “patent thickets” in which it is difficult or impossible for a drugmaker to know whether it will be sued for patent infringement once a new drug is produced. This could deter drugmakers from responding to an AdvancedMarkets incentive even if the guaranteed price was otherwise reasonable. A strong public domain would reduce this danger.

*Time to Act?* Ten years ago, neglected disease research was so under-funded that commercial firms had little incentive to find, let alone patent new targets or compounds. Existing and projected spending increases could easily change this calculation. Sponsors should act to preserve and expand the public domain before private patenting increases.

## VI. Conclusion

The continued infusion of new funds into neglected disease research is exciting. However, it also brings an urgent need to make choices and implement reforms. This paper has identified multiple areas where action is needed:

*Setting Strategy.* Sponsors must decide whether AdvancedMarkets, Virtual Pharma, or some combination of the two is likely to be the most cost-effective way to develop new drugs for neglected diseases. If sponsors adopt a Virtual Pharma model, they must further decide which institution(s) are likely to be most effective at each stage of the drug discovery process. Table 5 of this paper presents a benchmark strategy for organizing drug research using prizes, contracts, open source, and other non-traditional incentives.

*The Need for Evidence.* The debate between AdvancedMarkets and Virtual Pharma advocates has too often been left to ideology. The results have been inconclusive and unsatisfactory. This paper has argued that sponsors should pick whichever strategy is likely to contain costs. We have emphasized that the answer to this question will depend on specific factual questions such as (a) current uncertainties in the reward needed to elicit new drug discovery, and (b) the extent to which drugmakers can exploit their purchasing power to extract additional value from outsourced research. *These are relatively simple questions, well within the reach of a blue ribbon committee.* Sponsors should make answering them a top priority.

*A New Paradigm for Foundations.* Proofs of private sector efficiency usually assume the existence of profit-maximizing shareholders. There is no reason why foundations cannot play this same role for PPP research. First, however, the current system must be reformed so that foundations are both willing and able to de-fund PPPs that fail to perform. Foundations that doubt their ability to de-fund non-performing PPPs should avoid Virtual Pharma strategies.

*Enlarging the Public Domain.* Putting multiple new targets and drug compounds into the public domain will strengthen Virtual Pharma strategies by enhancing PPPs' ability to negotiate cost-effective R&D contracts for both patented and unpatented compounds. Less clearly, it may also make AdvancedMarkets incentives more effective.

*Empowering Local Regulators.* FDA requirements are an important driver of rich nation drug discovery costs. However, inefficient or irrelevant FDA requirements may make neglected disease research needlessly expensive. Building local and regional regulatory capacity is a powerful tool for reducing R&D costs.

*Understanding the Role of Patents.* PPPs frequently enter commercial partnerships in order to acquire new assets for their work. This tactic is short-sighted to the extent that sponsors end up paying for these assets in the form of

higher drug prices. PPPs should adopt detailed guidelines clarifying when patent rights do (and do not) benefit neglected disease research as a whole.

In practice, no real decision is likely to be perfect or free from doubt. Sponsors will face hard choices where the outcome cannot be guaranteed. Given that all known innovation institutions are imperfect, this result is hardly surprising. The key will be to understand not just that flaws exist, but to make a judgment about which flaws are truly important. Given that we must choose, which weaknesses are we best able to live with?

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<sup>1</sup> Andrew Farlow, “An Analysis of the Problems of R&D Finance for Vaccines and an Appraisal of Advance Purchase Commitments,” (Draft: April 21, 2004) at p. 21.

<sup>2</sup> Cf., Solomon Nwaka and Robert G. Ridley, “Virtual Drug Discovery and Development for Neglected Diseases through Private-Public Partnerships” (adopting terms “virtual drug discovery” and “virtual R&D).

<sup>3</sup> Quoted in Steven Weinberg, *Dreams of a Final Theory* (1994) at pp. 102, 128, 316.

<sup>4</sup> Of the 1,233 drugs licensed between 1975 and 1997, only 13 were for neglected diseases. Furthermore, most of these drugs were either developed outside the patent system or else were spin-offs of products created for other purposes. Thus, five came from veterinary research, two were modifications of existing medicines, and two were produced for the US military. Merrill Goozner, *The \$800 Million Pill: The Truth Behind the Cost of New Drugs* (Berkeley: University of California Press: 2004) at 245; Jean Lanjouw, “Big Ideas,” in *The Milken Institute Review* 6:71-78 (2004); Michael Kremer & Rachel Glennerster, *Strong Medicine: Designing Pharmaceutical Markets to Treat Neglected Diseases* (Princeton: 2004) at pp. 25-6.

<sup>5</sup> Farlow, “Analysis,” *supra*, at p. 16.

<sup>6</sup> *Id.* at p. 31 (incomplete information can persuade more (or fewer) firms to perform research than is scientifically efficient).

<sup>7</sup> Ceri Phillips and Guy Thompson, “What is A QALY?,” available at [www.evidence-based-medicine.co.uk](http://www.evidence-based-medicine.co.uk).

<sup>8</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 12 (quoting Nevio Zararia, WHO).

<sup>9</sup> Maurice McGregor, “Cost-Utility Analysis: Use QALYs Only With Great Caution,” *Canadian Medical Association Journal* 168:433 (2003) (surveys show that physicians value the impact of impotence on quality of life twenty to sixty percent less than patients do).

<sup>10</sup> Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry (1998), Chapter 3 at p. 9 (physicians often hesitate before trying drugs that offer only modest improvements over familiar products) available at <http://www.cbo.gov/shodoc.cfm?/index=655&dsequence=4>

<sup>11</sup> S. Maurer & S. Scotchmer, “[The Independent Invention Defense in Intellectual Property](#),” *Economica* 69:535 (2002).

<sup>12</sup> Congressional Budget Office, “Increased Competition,” *supra*, Chapter 3 at p. 7.

<sup>13</sup> *Id.* at p. 7. PhRMA claims that duplicative drugs cost approximately 90 percent as much as breakthrough drugs. Dean Baker, “Financing Drug Research: What Are the Issues?” (2004) at p. 20, available at [www.cepr.net](http://www.cepr.net).

<sup>14</sup> Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards* (1993) at p. 7 (deliberate imitation should produce shorter and more certain discovery periods). Available at <http://www.wvs.princeton.edu/cgi-bin/byteserv.prl/~ota/disk1/1993/9336/933603.PDF>.

<sup>15</sup> Congressional Budget Office, “Increased Competition,” *supra*, Chapter 3 at p. 7.

<sup>16</sup> *Id.* at Chapter 1, p. 7 and Chapter 3, p. 9 (Many physicians hesitate to try unfamiliar me-too drugs that are not clearly more effective and/or offer fewer side effects); Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Rewards* (1993) at pp. 3-4 (describing federal health care program procurement policies) and 300 (pioneer drugs typically maintain a roughly 40% market share five years after the underlying patent expires even though follow-on products tend to cost less).

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<sup>17</sup> Congressional Budget Office, “Increased Competition,” *supra*, Chapter 4, at p. 7; *Id.* at p. 5 (describing regulatory statutes that let manufacturers delay generic competition by launching new versions of existing products), 7 (describing statutes that provide for expedited consideration and approval of new drugs); and 8 (describing FDA regulations that establish the showing that would-be generic drug manufacturers must make to demonstrate safety and efficacy (“bioequivalence”).

<sup>18</sup> Congressional Budget Office, “Increased Competition,” *supra*, at Chapter 1, p 1 (Hatch-Waxman Act may have cut drugmaker revenues by about 12%).

<sup>19</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 2; Richard N. Foster, “Long Live the King,” in *The Milken Institute Review* 6:28-34 (2004) (“Over the past twenty years, Pharma’s investors have received the most rewarding returns of any sector in the US economy”); *but see*, Congressional Budget Office, “Increased Competition,” *supra*, Chapter 1 at p. 3 (Drug R&D continues to earn “roughly a normal rate of return . . . on average”).

<sup>20</sup> Press coverage in rich nations suggests that even sophisticated observers may not realize that patented drug prices are *supposed* to cover more than manufacturing costs. *See, e.g.*, Anon., “Prescriptions and Profits,” *60 Minutes* (March 14, 2004) (press report arguing criticizing drugmakers for charging prices that substantially exceed manufacturing costs). Available at <http://www.suddenlysenior.com/60minutesRxProfits.html>.

<sup>21</sup> Mattias Ganslandt, Keith E. Maskus & Elina V. Wong, “Developing and Distributing Essential Medicines to Poor Countries: The DEFEND Proposal,” *The World Economy* (Blackwell 2001) 24:785; J. Sachs, “Helping the World’s Poorest,” *The Economist* (14 Aug. 1999); Kremer & Glennerster, *Strong Medicine*, *supra*.

<sup>22</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at pp. 105 - 107. In practice, rewards could “increase somewhat faster” because of the danger that competitors could preempt the market and/or that delay would “use up patent life.” The former effect is especially large for early stage development, which is relatively easy to hide. *Id.* at 120.

<sup>23</sup> S. Scotchmer, *Innovation and Incentives* (MIT 2004) at pp. 1 - 11.

<sup>24</sup> Lilian Hilaire-Perez and Dominique Foray, “Inventing a World of Guilds: The Case of Lyons in the XVIII Century,” (2001), forthcoming in *Research Policy*.

<sup>25</sup> Defense Advanced Research Projects Agency, “DARPA Grand Challenge, available at <http://www.darpa.mil/grandchallenge/>.

<sup>26</sup> NASA, “Overview and Goals for Centennial Challenges,” available at [http://www.centennialchallenges.nasa.gov/cc\\_overview.pdf](http://www.centennialchallenges.nasa.gov/cc_overview.pdf)

<sup>27</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 87.

<sup>28</sup> Rogerson, W. (1994), “Economic incentives and the defense procurement process,” *J. Economic Perspectives*, 8:65-90; *see also*, Maurer and Scotchmer, “Procuring Knowledge,” *supra* at p. 16.

<sup>29</sup> *Id.* at p. 50

<sup>30</sup> Stephen Maurer & Suzanne Scotchmer, “Procuring Knowledge,” in Gary D. Libecap (ed.), *Intellectual Property and Entrepreneurship* (Elsevier 2004) at p. 11, pre-print available at <http://www.nber.org/papers/w9903>.

<sup>31</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at pp. 51-53.

<sup>32</sup> Farlow, “Analysis,” *supra*, at p. 101. *But see*, Joseph DiMasi, Ronald Hansen & Henry Grabowski, “The Price of Innovation: New Estimates of Drug Development Costs,” *Journal of Health Economics* 22:151 (2003) at p. 175 & n. 34 (reporting that seven firms recovered an average of only 2.0% of their R&D costs between 1999 and 2001). DiMasi *et al.* also cite Congressional data suggesting that orphan tax credits amount to less than one percent of total R&D costs. *Id.*

<sup>33</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 51.

<sup>34</sup> *Id.* at 50 (public programs can “throw good money after bad.)

<sup>35</sup> *Cf.* Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 70 (buyouts are difficult to reverse if purchased drugs prove unsatisfactory).

<sup>36</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 69.

<sup>37</sup> *Id.* at p. 70.

<sup>38</sup> *Id.* at pp. 71-72.

<sup>39</sup> *Id.* at pp. 71-72.

<sup>40</sup> *Id.* at p. 71.

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<sup>41</sup> World Bank Task Force on Accelerating the Development of an HIV/AIDS Vaccine for Developing Countries, “HIV Vaccine Industry Study, October – December 1998” (Draft dated 20 March 2000), available at [http://www.iaen.org/files.cgi/103\\_batson.pdf](http://www.iaen.org/files.cgi/103_batson.pdf) (2000)/

<sup>42</sup> *Id.*

<sup>43</sup> Conventional patents cannot provide a greater reward to inventors than consumers are willing to pay for her invention. TIPRs break this link. The requirement goes back to England’s Statute of Monopolies (1623) 21 Jac. 1, c. 3. Some case law suggests that Congressional attempts to break this link are *ipso facto* unconstitutional. See, e.g., *Hensley Equip. Co. v. Esco Corp.*, 383 F.2d 252, 260 (5th Cir. 1967) (“Neither Congress nor the courts may exercise or apply the patent authority in such manner as to give a patentee more than the rewards of his discovery.”)

<sup>44</sup> Farlow, “Analysis,” *supra*, at p. 33. The inefficiency is greater for technologies that involve cumulative and complementary discoveries by many actors. *Id.* at p. 10. (“Whether prize funds are appropriate for technology of a more cumulative and complementary nature, in a high IPR environment, with later rounds of technology ‘reading off’ dozens, even hundreds, of earlier rounds of patents, is not immediately clear.”)

<sup>45</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 6 (commercial firms tend to pursue separate R&D efforts when it would be more efficient to share information and/or collaborate).

<sup>46</sup> Farlow, “Analysis,” *supra*, at p. 37 - 38.

<sup>47</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at pp. 83 - 84. The problem is not limited to corruption. If sponsors do not pay the full cost of the drug, manufacturers can offer additional resources (either in cash or in kind) to induce them to purchase more than they would at an unsubsidized price. Once again, sponsors and manufacturers split the subsidy. In this case, the sponsor spends its share of the subsidy on helping LDCs. However, the manufacturer’s share is still lost to the system and does nothing to benefit LDCs.

<sup>48</sup> One possible counterargument is that pay-as-you go systems allow foreign aid and science bureaucrats to exercise greater control. Kremer, “Making Vaccines Pay,” *supra*. This argument necessarily assumes that these same bureaucrats are not intimidated by the prospect of being blamed for failures.

<sup>49</sup> Kremer, “Making Vaccines Pay,” *supra*.

<sup>50</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines: A Practical Plan to Spark Innovation for Global Health*, (Center for Global Development & Global Health Policy Research Network: 2002) (consultation draft) at p. 33 (“there need not be a trade-off between push and pull policies”; it might be “affordable and desirable” for PPPs to continue operations).

<sup>51</sup> Roy Widdus and Katherine White, “Combating Diseases Associated With Poverty,” (Initiative on Public-Private Partnerships for Health 2004) at p. 32 (“pull” mechanisms would benefit PPPs by making commercial firms more confident that a market exists).

<sup>52</sup> Farlow, “Analysis,” *supra*, at p. 20 (quoting Prof. Kremer: research is likely to have the same discounted cost whether it is financed at the front end through government grants or the back end through payments for a successful vaccine.)

<sup>53</sup> See, e.g. Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 72 (“[w]ith a purchase program, on the other hand, no public funds are spent unless the desired product is developed”); AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at pp. 7, 38 (commitment would “have no impact on [sponsors’] budget until a vaccine is developed.”).

<sup>54</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at pp. 7, 38 (AdvancedMarkets “... does not call upon donors to spend more than they otherwise would; but it does increase the value of that spending); *Id.* at p. 6 (arguing that commitment makes existing spending more productive by making it more predictable).

<sup>55</sup> Kremer, “Making Vaccines Pay,” *supra*

<sup>56</sup> Robert G. Ridley, “Product Development Public-Private Partnerships for Diseases of Poverty,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 202. Other R&D spending estimates are slightly higher than Ridley’s figures. AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 24 (total resources for vaccines against HIV, TB, and malaria are “far less” than \$1bn per year.), 26 (total global funding for malaria vaccines are about \$65 million per year); Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 5 (quoting Trevor Jones,

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Association for British Pharmaceutical Industries ) (asserting that \$564 million was spent on drug R&D for developing world diseases in 2001).

<sup>57</sup> Scott Hensley, “Wyeth is Upbeat About Innovation at Its Drug Labs,” *Wall Street Journal* (June 3 2003), p. D.3 (Wyeth has a \$2.1 billion R&D budget); Thomas M. Burton, “Abbott Says Wait for Drugs Will be Worth It,” *Wall Street Journal*, May 30 2003 (Abbott has a \$1.1 billion R&D budget; Merck and Eli Lilly each have budgets of “over \$2 billion”); Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) (Pfizer had a \$5.3 billion R&D budget 2003).

<sup>58</sup> Sarah Houlton, “Drugs for Neglected Diseases: A Non-Profit Partnership Will Create a Structure to Develop Therapies That are Badly Needed in Poor Countries,” *Pharmaceutical Executive*, (Aug. 1 2003) at p. 28 (DNDi hopes to spend \$25 million per year over the next decade, deliver six or seven new drugs, and keep its pipeline stocked with new candidates).

<sup>59</sup> A. Towse, J. Mestre-Ferrandiz & O. Renowden, “Estimates of the Medium Term Financial Resource Needs for Development of Pharmaceuticals to Combat ‘Neglected Diseases,’” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 92 (Commercial firms may have up to 100 drugs in the preclinical and clinical pipeline at any one time); Scott Hensley, “Wyeth is Upbeat About Innovation at Its Drug Labs,” *Wall Street Journal* (June 3 2003), p. D.3 (During the 1990s, Wyeth moved roughly three drugs per year into full development. Since then, it has increased the rate to approximately twelve per year); Ridley, “Product Development,” *supra*, at pp. 202, 205 (ten percent estimate).

<sup>60</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 89 (a malaria vaccine could generate as much as \$200 million in sales to rich nation travelers, tourists, and military personnel).

<sup>61</sup> The Global Alliance for TB Drug Development, *Economics of TB Drug Development* (2001), at p. 26. Available at [http://66.216.124.114/pdf/Economics%20Report%20Full%20\(final\).pdf](http://66.216.124.114/pdf/Economics%20Report%20Full%20(final).pdf) (estimated private market for TB drugs).

<sup>62</sup> Ganslandt *et al.*, “The DEFEND Proposal” *supra*, at p. 20 & n. 24. Some industry observers believe that existing markets are large enough to support development of an AIDS vaccine. Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 13 (quoting Franz van den Boom: “[P]harma does not need guarantees of purchases.”); Ridley, “Product Development,” *supra*, at p. 192 (HIV/AIDS antibiotics and antivirals are commercially motivated).

<sup>63</sup> DNDi, *DNDi Business Plan*, (March 18 2003), available at [http://www.dndi.org/cms/public\\_html/images/article/267/DNDiBusinessPlan.pdf](http://www.dndi.org/cms/public_html/images/article/267/DNDiBusinessPlan.pdf)

<sup>64</sup> Ridley, “Product Development,” *supra*, at p. 198 (malarone).

<sup>65</sup> Farlow, “Analysis,” *supra*, at p. 138 & n. 262.

<sup>66</sup> For example, the total GDP of sub-Saharan Africa is approximately \$285 billion. At US prices, delivering AIDS drugs to sub-Saharan Africa would cost \$299 billion. Ganslandt *et al.*, “The DEFEND Proposal,” *supra*, at p. 15 & n. 20. This comparison is admittedly unrealistic to the extent that it ignores the possibility of tiered pricing. However, Section IV.E suggests that tiered pricing would reduce LDC drug prices by, at most, an order of magnitude. For this reason, the basic conclusion is robust.

<sup>67</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 11.

<sup>68</sup> Drugmakers have devoted enormous resources to resisting Congressional subpoenas in the past. From 1977 to 1983, large drugmakers fought five court cases. The issue ultimately went to the US Supreme Court. *Bowsher v. Merck*, *Office of Technology Assessment*, 460 US 824, 843 (1983); *See also*, Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 286-88; Robert Pear, “Research Cost for New Drugs Said to Soar,” *New York Times* (Dec. 1 2001), p. C.1 (“Federal auditors usually have access to the records of federal providers. However, drug companies have resisted this for decades”); Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (Pharma “is one of the world’s most lucrative and secretive industries.” Its cost argument has “rarely been put under a microscope because the industry will not divulge the costs of researching and developing a particular drug”).

<sup>69</sup> The study is based on survey data from ten anonymous firms based on 68 randomly selected drugs that received initial testing in humans anywhere in the world between 1983 and 1994. Development costs were obtained through 2000. DiMasi *et al.*, “The Price of Innovation,” *supra*, at pp. 156-158.

<sup>70</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 166.

<sup>71</sup> Robert Pear, “Research Cost for New Drugs Said to Soar,” *New York Times* (Dec. 1 2001), p. C.1 (quoting Congressman Henry Waxman: “The basic problem is that all pharmaceutical costs, including

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research, are in a black box, hidden from view. There is no transparency. That's the cause of all the skepticism regarding drug research costs and pricing.”).

<sup>72</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 6. Drugmakers are less likely to misreport phase specific development times and success rates, which are known to the FDA. *Id.*

<sup>73</sup> Robert Pear, “Research Cost for New Drugs Said to Soar,” *New York Times* (Dec. 1 2001), p. C.1.

<sup>74</sup> *Id.*; *see also*, Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 65 (“Although the cost estimates of bringing an NCE to market are imprecise and potentially biased, corroborative evidence ... suggests that they are not grossly overestimated.”)

<sup>75</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 11, 284 & Appendix D (Congress is politically reluctant to issue subpoenas. Enforcing subpoenas “would be very costly and take many years.”). In principle, Congress could break the impasse by examining drugmaker accounting records in confidence. However, a similar compromise fell through in the 1980s after some representatives demanded that any information be made public. *Id.* at p. 285.

<sup>76</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at pp. 37, 52, 54.

<sup>77</sup> *Id.* at pp. 37, 48 and Exhibit 23. Global Alliance notes that the \$5.3 million figure is a minimum estimate. Global Alliance does not an upper limit.

<sup>78</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 162 and Table 1.

<sup>79</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at pp. 37 - 38, 65.

<sup>80</sup> *Id.* at p. 38. Global Alliance’s estimate is based on PhRMA’s assertion that discovery costs account for roughly one-fourth of per-drug R&D costs. *Id.*

<sup>81</sup> *Id.* at p. 66.

<sup>82</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 169.

<sup>83</sup> Towse *et al.* “Estimates of Medium Term Financial Resource Needs,” *supra*, at pp. 91-93.

<sup>84</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 89.

<sup>85</sup> E. Berndt *et al.*, “Advanced Markets for a Malaria Vaccine: Estimating Costs and Effectiveness” (2005) (unpublished: copy on file with the author).

<sup>86</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 162 (The number of procedures administered to patients in Phase III increased 27% between 1990 and 1997).

<sup>87</sup> *Id.* at p. 168.

<sup>88</sup> *Id.* at p. 173.

<sup>89</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 1 (“The cost of bringing a new drug to market is very sensitive to changes in science and technology, shifts in the kinds of drugs under development and changes in the regulatory environment. All of these changes are occurring fast. Consequently, it is impossible to predict the cost of bringing a new drug to market today from estimate costs for drugs whose development began more than a decade ago”), 66 (“The rapid increase in inflation-adjusted R&D cash outlays over the relatively short observed time span separating Hansen’s and DiMasi’s studies illustrates how quickly such costs can change and how sensitive such costs are to changes in R&D success rates over time.”).

<sup>90</sup> Richard Spivey, Louis Lasagna, Judith Jones, William Wardell, “The US FDA in the Drug Development, Evaluation and Approval Process,” in J.P. Griffin and J. O’Grady (eds.), *Textbook of Pharmaceutical Medicine* (London: BMD Books 2002) at p. 717; Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (Companies hope that improved technology and spending increases will lead to more drugs ten years from now. In the long run, science may be able to predict toxicity and effectiveness by studying how a drug affects genes. This would reduce failure rates in animals and humans. In the short run, it has left the industry inundated by targets and data and increased the failure rate by leading companies to start trials before they understand what the data are telling them); DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 182 (“Cost growth may be driven by new technologies that generate many targets that are poorly understood. Eventually, science will be able to narrow the list of these candidates”). Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (“Automation has broadened the list of potentially useful compounds but so far has not delivered commensurate growth in safe and effective drugs”).

<sup>91</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 158 (Variability of drug R&D costs tends to increase with development phase and the amount of time a drug spends in testing).

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<sup>92</sup> Office of Technology Assessment, *Pharmaceutical R&D, supra*, at pp. 56 - 57 (further methodological refinements will probably yield only modest improvements). The Office of Technology Assessment suggested that future studies might control for differences in accounting practices between firms. However, it conceded that adding these refinements was not likely to produce “very different” results. *Id.* at p. 5.

<sup>93</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002); DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 181. DiMasi speculates that these factors may explain recent increases in clinical trial costs. *Id.*

<sup>94</sup> P. Landers, “Drug Industry’s Big Push Into Technology Falls Short,” *Wall Street Journal* (Feb. 24, 2004); World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (lack of animal models).

<sup>95</sup> *Id.*

<sup>96</sup> *Id.* (safety and efficacy tests for an HIV vaccines would probably have to be repeated in different target populations.)

<sup>97</sup> *Id.* at pp. 38, 52 (lack of historical experience makes it difficult or impossible to estimate costs of drug prior to human testing).

<sup>98</sup> Global Alliance, *Economics of TB Drug Development, supra*, at p. 38.

<sup>99</sup> A. Sander and R. Widdus, “The Emerging Landscape of Public-Private Partnerships for Product Development,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 108 (HHVI, MVI, and IAVI are trying to develop the first vaccines for specific diseases. Microbicides are a fundamentally new type of product).

<sup>100</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002); Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1.

<sup>101</sup> Global Forum for Health Research, *The 10/90 Report on Health Research: 2003-2004* at p. 195, available at [www.globalforumhealth.org](http://www.globalforumhealth.org) (TB R&D has been at “a virtual standstill” since the 1960s); Sander and Widdus, “Emerging Landscape” *supra*, at p. 108 (TB science has not improved “over many decades.”).

<sup>102</sup> DNDi, *DNDi Business Plan, supra*, at p. 10. (Describing DNDi plans to develop projects for which a registration dossier has been begun but not yet completed; adapt existing drugs to new uses, new populations and indications (e.g., pediatric, long-acting, new delivery modes); and adapt existing drugs to new geographic regions and/or formulations.)

<sup>103</sup> DNDi, *DNDi Business Plan, supra*, at p. 20.

<sup>104</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines, supra*, at p. 18; A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 92 (Vaccines tend to be more expensive to develop because (a) most easy vaccines may already have been found, suggesting that future failure rates are likely to be high, (b) vaccine programs usually have smaller portfolio sizes, which may force abandonment in preclinical stages, (c) vaccines usually face greater uncertainty with respect to efficacy and toxicity, and (d) vaccine trials usually require much larger cohorts).

<sup>105</sup> Global Alliance, *Economics of TB Drug Development, supra*, at pp. 52, 56, Appendix D, and Appendix E-2. (estimating that Phase I through III trials would cost \$26.6 million in the developed world but \$9.9 million in an LDC); World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (AIDS vaccine trials might cost less in LDCs because high infectivity rates mean that smaller cohorts can be used); *Id.* (AIDS trials might cost more in LDCs because of pose political and infrastructure barriers).

<sup>106</sup> World Bank Task Force, “HIV Vaccine Industry Study,” *supra*. Infrastructure costs are likely to be highly variable from country to country. Many LDCs including India, Uganda, and South Africa have substantial capability to meet regulatory standards. Global Alliance, *Economics of TB Drug Development, supra*, at p. 52.

<sup>107</sup> Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 191 (Vaxgen paid roughly the same per-patient costs for Phase III AIDS trials in Thailand as it did for parallel trials in the US, Canada, and the Netherlands).

<sup>108</sup> Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (Vertex Pharmaceuticals spent \$50 million per drug to advance seven products to Phase II trials, “a fraction of the usual cost.”). Global Alliance claims that time and cost needed to find a

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promising lead compound depends, *inter alia*, on the capacity of R&D facilities and the availability of advanced technologies. Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 38.

<sup>109</sup> Anon., “Maximizing Productivity: Getting More Bang for Your R&D Buck,” ResearchandMarkets.com (consulting report) (Feb. 20 2003) (Using the Internet to recruit patients can reportedly reduce per patient costs from \$1,200 to \$300).

<sup>110</sup> Farlow, “Analysis,” *supra*, at p. 137 (Price guarantee should be aimed at biotechs, which are substantially more risk-tolerant and might be willing to enter the market at a lower price). The point was also made in draft versions of Kremer & Glennerster, *Strong Medicine*, *supra*, (MS on file with the author) at p. 100.

<sup>111</sup> See, e.g., Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2 2003) at p.17 (Asian chemical companies routinely sell process development and manufacturing services at a five percent discount compared to rich nation firms).

<sup>112</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 65 (there is a wide range of opinions as to whether a malaria vaccine is feasible. Some companies have decided not to invest on scientific grounds); World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (during the 1990s, smaller companies were scientifically optimistic about novel AIDS vaccines but faced a “market judgment” that blocked rapid development).

<sup>113</sup> *Id.* (biotech firms are more optimistic than existing vaccine makers.)

<sup>114</sup> DiMasi *et al.*, at pp. 171-172 (Mean out-of-pocket approved cost for approved drugs was \$176.5 million vs. 130.2 million for drugs that were not approved.)

<sup>115</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 171 (reporting “a tendency to direct more resources, possibly by conducting more studies concurrently, to investigational drugs as a whole”) (emphasis supplied).

<sup>116</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 172.

<sup>117</sup> Farlow, “Analysis,” *supra*, at p. 138.

<sup>118</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 169.

<sup>119</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 66.

<sup>120</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 2.

<sup>121</sup> Ridley, “Product Development,” *supra*, at p. 199 (\$200 million); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 4 (1997 estimate: \$300 million); Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 88 (quoting Robbins-Roth (2000)).

<sup>122</sup> Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 925.

<sup>123</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at 38.

<sup>124</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at 91 (citing DiMasi).

<sup>125</sup> Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (drugmakers routinely outsource basic drug discovery, animal and human testing, process development, and manufacturing).

<sup>126</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 173. Of the top ten drugs launched in 2001, only two came from the portfolios of Big Pharma. Lisa Jarvis, “Fine Chemicals Producers Need to Look Beyond Size,” *Chemical Market Reporter*, at p. 8 (Oct. 22 2001).

<sup>127</sup> Peter Landers, “Cost of Developing New Drug Increases to About \$1.7 Billion,” *Wall Street Journal* Dec. 8 2003, p. B.4; Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (Industry analysis claim that big drug companies “will increasingly become the marketers and coordinators of work done by others.”); *Id.* (quoting Accenture Consulting executive: “We think the old model of having everything under your own roof, a completely integrated monolithic organization, is not feasible”); Lorne Bleriot, “Chasing the Bald Eagle,” *Pharmaceutical Technology Europe* (June 1, 2001) at p. 65 (reporting that major and medium size pharmas purchase contract research from early stage products through maturity and that companies are beginning to spin off R&D groups as separate entities); David A. Shaywitz & Dennis Ausiello, “Can Drug Giants Survive the Biomedical Revolution?” *Wall Street Journal* (Feb. 8 2000), A26 (big companies merge to put more drugs into the pipeline, smaller companies feel pressure to establish partnerships).

<sup>128</sup> Phil Norris, *Pharmaceutical Technology Europe*, p. 15 (March 1 2003) (virtual pharmas should outsource discovery, research, clinical and process development, commercial manufacturing and supply while retaining portfolio management, study design, clinical supplies, dossier compilation, and regulatory

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communications); Gordon Graff, "Custom Chemical Manufacturing," *Purchasing* (March 4, 2004), p. 24C3 (Virtual Pharma has proprietary products or technologies but no manufacturing facilities).

<sup>129</sup> Hannah Kettler & Karen White, "Valuing Industry Contributions to Public-Private Partnerships for Health Product Development," (Initiative on Public-Private Partnerships for Health 2003) at p. 7 (current Virtual Pharmas include DevCo Pharmaceuticals, Poxen Inc, Arachnova Ltd, and Fulcrum Pharmaceuticals).

<sup>130</sup> Lorne Bleriot, "Chasing the Bald Eagle," *Pharmaceutical Technology Europe* (June 1, 2001) at p. 65.

<sup>131</sup> Office of Technology Assessment, *Pharmaceutical R&D, supra*, at p. 10.

<sup>132</sup> *Id.* at p. 10.

<sup>133</sup> Sander and Widdus, "Emerging Landscape" *supra*, at p. 99 ("A risk with a virtual R&D/contract model is that contractors may not have an incentive to spot early problems in their research. Also, there may not be anyone asking the integrating questions across the various steps. Coordinating whether the product could be manufactured at a reasonable price, whether the regulators would approve such a product, whether and how the financing will be available to procure such a product all require advanced coordination and project management skills of a very complex process that may be happening at different times for different candidates."), 109 (PPPs must "ask tough and integrative questions, anticipate future stages, update and prune the portfolio.")

<sup>134</sup> Ridley, "Product Development," *supra*, at p. 200 (Public sector agencies developed and manufactured early vaccines; today, they continue to develop and produce antidotes and vaccines against chemical and biological warfare agents); Kremer & Glennerster, *Strong Medicine, supra*, at pp. 46 - 47 (Walter Reed Army Hospital developed a successful meningococcal vaccine in the 1960s); Office of Technology Assessment, *Pharmaceutical R&D, supra* at p. 314 (Walter Reed has managed a malaria program since the 1960s); N. Covert, "Cutting Edge: A History of Fort Detrick" (2000) (describing US Army success in developing vaccines against Argentine hemorrhagic fever, Venezuelan equine encephalitis, Rift Valley fever, tularemia, infant botulism, and other diseases.), available at [http://www.detrick.army.mil/detrick/cutting\\_edge/index.cfm?chapter12](http://www.detrick.army.mil/detrick/cutting_edge/index.cfm?chapter12).

<sup>135</sup> World Bank Task Force, "HIV Vaccine Industry Study," *supra*.

<sup>136</sup> *Id.*

<sup>137</sup> Farlow, "Analysis," *supra*, at p. 17 (fewer than 200 private sector scientists are working on HIV vaccines, including programs paid for by the public sector).

<sup>138</sup> Global Forum for Health Research, *10/90 Report, supra*, at p. 195 (TB research has been at "a virtual standstill" since the 1960s); Sander and Widdus, "Emerging Landscape" *supra*, at p. 108 (TB science has not improved "over many decades"); Jeff Garth & Sheryl Gay Stolberg, "Drug Makers Reap Profits on Tax-Backed Research," *New York Times* (April 23, 2000), p. 1.1 (basic research can last two to twelve years).

<sup>139</sup> Survey evidence suggests that genetics researchers refuse to share data about ten percent of the time. Geneticists explained their refusal to share data as effort Required to Produce Requested Information or Materials (80%), Need to Protect Graduate Student's, Post-Doctoral Fellow's, or Junior Faculty's Ability to Publish (64%), Need to Protect Own Ability to Publish (53%), Financial Cost of Actually Providing Materials or Information Transfer (45%), Likelihood that Other Person Will Never Reciprocate (28%), Need to Honor Requirements of the Industrial Sponsor (27%), Need to Preserve Patient Confidentiality (23%), Need to Protect the Commercial Value of Results (21%). E. Campbell, B. Clarridge, M. Gokhale, L. Birenbaum, S. Hilgartner, N. Holtzman, D. Blumenthal, "Data Withholding in Academic Genetics: Evidence from a National Survey," *Journal of the American Medical Association* **287**:473 (2002).

<sup>140</sup> A. Patrinos & D. Drell, "The Times They Are A-Changin,'" *Nature* **417**:589 (2002).

<sup>141</sup> Mark Swindells, "How to Discover Drug Targets in Genomics Databases," *Innovations in Pharmaceutical Technology* 00: 69-74 (2000) available at <http://www.pharmacolome.com/publications/010900.htm>.

<sup>142</sup> Farlow, "Analysis," *supra*, at p. 36 (arguing that patent system works poorly for early research that is excessively complicated and whose value is hard to determine); Kremer & Glennerster, *Strong Medicine, supra*, at p. 45 (arguing that neglected disease R&D should imitate rich nation programs, which depend on a combination of push (public funding) for basic research and pull programs (patents) for applied research).

<sup>143</sup> Schmid, "Portfolio Management in the Pharmaceutical Industry," *supra*, at p. 158 ("representative illustration" of early attrition listing 50% chance of transition from "idea" to "hit"); Widdus and White, "Combating Diseases Associated With Poverty," *supra*, at p. 91 (quoting 30% MMV estimate for "early

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discovery”); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 925 (30% transition probability for “exploratory early discovery”); Andrej Sali (time frame is typically “a year or two”) (personal communication)..

<sup>144</sup> Peter Gwynne and Garby Neebener, “Drug Discovery and Biotechnology Trends,” *Science* **302**: 1421 (2003), available at [http://www.sciencemag.org/feature/e-market/benchtop/ddbt\\_112103.shl](http://www.sciencemag.org/feature/e-market/benchtop/ddbt_112103.shl); Andrew Pollack, “Despite Billions for Discoveries, Pipeline of Drugs is Far from Full,” *New York Times* (April 19 2002), p. C.1 (“Until now, virtually all drugs have been directed at an estimated 500 proteins in the body. But by sifting through the human genome, companies are finding thousands of genes that produce previously unknown proteins that might be involved in the disease.”); David A. Shaywitz & Dennis Ausiello, “Can Drug Giants Survive the Biomedical Revolution?” *Wall Street Journal* (Feb. 8 2000), A26. (To date, drug industry has concentrated on about 500 proteins of the 100,000 estimated to exist in the human genome.)

<sup>145</sup> Andrej Sali (personal communication).

<sup>146</sup> Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (A 1995 MIT study found that 11 of the 14 most medically significant drugs produced since 1970 had their roots in studies paid for by the government. A 1997 NSF study found that half of all studies cited in patents were paid for by government and academia and only 17 percent by industry.)

<sup>147</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) (Pfizer searched the scientific literature and talked to academic scientists to find targets that induced pituitary gland activity); Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’ Process for Product Concepts/Candidate Products and Possible Improvements in It,” in Widdus and White, “Combating Diseases Associated With Poverty,” at p. 165.

<sup>148</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 25.

<sup>149</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 313 (National Institute of Child Health and Human Development provides contract support for programs to discover, develop, and clinically evaluate new contraceptive pharmaceuticals).

<sup>150</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 6.

<sup>151</sup> Russ Altman, personal communication (commercial drugmakers often have useful information about the existence of “dry holes”).

<sup>152</sup> Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), at p. 1.1.

<sup>153</sup> *Id.*

<sup>154</sup> A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 91; Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 924.

<sup>155</sup> P. Landers, “Drug Industry’s Big Push Into Technology Falls Short,” *Wall Street Journal* (Feb. 24, 2004).

<sup>156</sup> PhRMA, *Profile: Pharmaceutical Industry* (2004), at p. 34.

<sup>157</sup> Glaxo spent \$500 million to purchase a combinatorial chemistry company several years ago. Similarly, Pfizer has spent more than \$600 million to make sure that the chemicals in its libraries are “more diverse” and “drug like.” Senior Vice President Martin Mackay argues that a higher percentage of compounds are now making it through each stage of testing, although he concedes that “[t]he proof of the pudding will be in 10 years’ time.” P. Landers, “Drug Industry’s Big Push Into Technology Falls Short,” *Wall Street Journal* (Feb. 24, 2004).

<sup>158</sup> Andrej Sali (personal communication). Searches can deliver rough results within a few weeks. *Id.*

<sup>159</sup> Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), at p. 1.1 (NIH paid for animal studies that showed that natural prostoglandins could cure glaucoma).

<sup>160</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 23, 37.

<sup>161</sup> *Id.* at p. 25

<sup>162</sup> Global Forum for Health Research, *10/90 Report*, *supra*, at p. 197 (Drug developed for skin and upper respiratory tract infections and pneumonia shows activity against TB); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 25 (compound for treating athlete’s foot may treat Chagas Disease.)

<sup>163</sup> Andrej Sali (personal communication).

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<sup>164</sup> Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 927.

<sup>165</sup> Pharmacia reportedly paid Columbia University a lump sum payment of between \$100,000 and \$150,000 for work demonstrating that natural prostaglandins could treat glaucoma. The company later paid a further \$20 million in royalties. No drug was ever approved. Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1.

<sup>166</sup> Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 925.

<sup>167</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 164 (government agencies, NIH, and TDR operate screening facilities that give basic researchers a way to check product ideas and compounds); Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 311. (NIH’s Cancer Development Therapeutics Program screens and evaluates new compounds submitted by outside researchers, including industry); *Id.* at p. 314. (Walter Reed possesses the capability to discover, develop and evaluate new compounds).

<sup>168</sup> Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (Pharmacia spent tens of millions to find a synthetic prostaglandin); Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 22 (Nine chemists spent three years developing CRA-3316 family of compounds. Assuming \$250,000 per chemist per year, the dollar value of these services was \$2.3 million); Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2 002) (from the time that Pfizer decided to develop compound, it took only nine months to find a drug safe enough to test in humans. The company had never performed the task so quickly); A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 91 (55% transition probability); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 924 (same); Schmid, “Portfolio Management in the Pharmaceutical Industry,” *supra*, at p. 158 (70% transition probability shown as “representative illustration”).

<sup>169</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 164.

<sup>170</sup> Iaian Cockburn, “Comments,” in *The Milken Institute Review* 6:87-92 (2004) (“The involvement of the National Institutes of Health in screening for cancer drugs in a more-or-less commercial mode was largely unsuccessful. Nor have the well-intentioned efforts by the WHO to develop treatments and vaccines for neglected diseases worked well.”)

<sup>171</sup> Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at pp. 920, 923; Cynthia Challenger, “Smaller Fine Chemicals Players Find Their Niche,” *Chemical Market Reporter*, at p. FR10 (Sept. 30 2002). A good example of outsourcing is Peakdale Molecular (UK), which designs and develops chemicals under contract to support clients’ drug discovery programs. Pfizer currently has a multi-year agreement with Peakdale. Pfizer uses Peakdale’s compounds to supplement its own in-house chemistry programs.) Cynthia Challenger, “The Balancing Act of Small to Medium Sized Custom Manufacturers,” *Chemical Market Reporter* (April 14 2003).

<sup>172</sup> Schmid, “Portfolio Management in the Pharmaceutical Industry,” *supra*, at p. 156 (industry has “partial insights” into why projects fail. Although winners cannot be selected, some losers can be discarded on the basis of technical infeasibility before any physical work has started); Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 5. (“The one thing you learn in the industry is how to make a molecule ‘drugable.’” Academic institutions and governments lack this expertise); Mark B. McClellan, “View from the Iron Triangle,” in *The Milken Institute Review* 6:79-86 (2004) (Drug absorption and kinetics, interactions, toxicities, and manufacturing concerns are “more an art than a science today.”);

<sup>173</sup> Schmid, “Portfolio Management in the Pharmaceutical Industry,” *supra*, at p. 156 (Drug companies have also invested in various technologies to identify and discard weak candidates as soon as possible. Examples include computer simulations of compound-target interactions, large databases that link compound structures to toxicity problems, and test tube models that mimic disease processes).

<sup>174</sup> Anon., “Maximizing Productivity: Getting More Bang for Your R&D Buck,” ResearchandMarkets.com (consulting report: executive summary) (Feb. 20 2003) ( companies should add “marketing specialists” to R&D teams at the earliest possible stage); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 23 (Drugmakers usually add marketing specialists to R&D teams at the pre-clinical stage).

<sup>175</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 3. By 2005, pharmaceutical companies estimate that 50% of all income will come from products developed outside their organizations. *Id.*

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<sup>176</sup> Vanessa Fuhrmans, “Non-Profit Alliance will Pay Chiron for Rights to a Potential TB Drug,” *Wall Street Journal*, February 1, 2002 p. B.4 (Global Alliance for TB purchased development rights to commercial compounds at *in vitro* testing stage).

<sup>177</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 81 (UNICEF only purchases vaccines that are “prequalified” by WHO).

<sup>178</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 64.

<sup>179</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 164.

<sup>180</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at pp. 40 – 45 (preclinical studies would cost \$4.9 – 5.3 million and last 3 – 6 months); Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2 002) (Pfizer conducts clinical tests of safety and effectiveness on fewer than half of the drugs that its scientists investigate “in earnest”); Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 22 (Nine chemists spent three years developing CRA-3316 family of compounds. Assuming \$250,000 per chemist per year, the dollar value of these services was \$2.3 million); World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (consulting firm estimate for AIDS vaccine: Research/pre-clinical: three years, \$10 million); DNDi, *DNDi Business Plan*, *supra*, at p. 19 (oredevelopment will take two years and suffer from a 37% attrition rate); Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (preclinical discovery can account for up to 20 - 25 percent of a company’s R&D budget for individual drugs); PhRMA, *Profile: Pharmaceutical Industry* (2004), p. 43 (member firms spent about 33.8% of their R&D dollars on prehuman/preclinical testing in 2002. The figure is almost certainly understated since 11.3% of PhRMA’s data was “uncategorized.”); Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) (from the time that Pfizer decided to develop compound, it took only nine months to find a drug safe enough to test in humans. A very short time period.); A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 92 (reporting transition probability estimates ranging from 0.5 to 0.63, with one outlier at 0.10); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 924 (transition probability of 0.55).

<sup>181</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 5.

<sup>182</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 162.

<sup>183</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 311 (NIH’s Cancer Development Therapeutics Program supports extramural preclinical drug discovery and development.), 312-13 (NIH’s Antimicrobial Chemistry Program provides intramural program to screen compounds submitted by researchers outside the government. It also provides research support for designing and testing new compounds.), 313 (NIH’s Anticonvulsant Drug Program has funded preclinical, clinical investigations into new drugs to treat seizures); Spivey *et al.*, “The US FDA in the Drug Development,” *supra*, at p. 706 (NIH entities such as National Cancer Institute, cooperative cancer study groups, or AIDS Cooperative Trials Group often sponsor preclinical tests leading to an IND).

<sup>184</sup> Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 706.

<sup>185</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 64 & table 3-7 (surveying three commercial breeders and eleven laboratories to determine the cost of outsourced animal toxicity and safety testing): The Global Alliance for TB Drug Development, *Economics of TB Drug Development* (2001), at p. 40 (Detailed preclinical cost estimates based on survey of contract research organizations specializing in microbiology, toxicology, and drug metabolism.). Interestingly, the OTA study suggests that quoted prices frequently differ by a factor of two. No reason was given for the anomaly.

<sup>186</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) (Rat testing “was crucial in convincing management to proceed from research into the development of medicine that could be tested in humans”).

<sup>187</sup> Alexander Kohn, *False Prophets* (Blackwell 1986), at pp. 179-80 (FDA spot checks on drug and testing labs during the 1980s revealed shredding of documents, underreported dead rats, false claims that rat carcasses were too decomposed to do autopsies, and misreporting dead animals as alive and *vice versa*. An EPA survey of 900 studies performed by one commercial lab concluded that most were invalid); William Broad & Nicholas Wade *Betrayers of the Truth* (Simon & Schuster, New York 1982), at pp. 81-83 (FDA rejected company’s animal testing data *in toto* because of widespread data fabrication).

<sup>188</sup> Kohn, *False Prophets* at 179 (“Revolving door” employment practices between drugmakers and testing labs encourage contract workers to suppress unfavorable data).

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<sup>189</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 10 (Unigene licensed a preclinical drug to GSK for \$150 million in 2002. The deal included upfront payments, milestone payments, and royalties); *Id.* at p. 21 (Rigel licensed an antiviral hepatitis c vaccine to Questcor for \$1 million in cash and stock followed by up to \$10m in milestone payments); Peter Landers & Joanne S. Lublin, “Under a Microscope: Merck’s Big Bet on Research By Its Scientists Comes Up Short.” *Wall Street Journal* (Nov. 28, 2003), p. A.1 (Merck purchased a preclinical diabetes drug in 1999); Vanessa Fuhrmans, “Non-Profit Alliance will Pay Chiron for Rights to a Potential TB Drug,” *Wall Street Journal*, February 1, 2002 p. B.4 (Global Alliance purchased the LDC rights to a potential TB drug from Chiron in 2002. The deal involved an undisclosed up-front payment plus milestone payments if the drug continued to make progress in trials).

<sup>190</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 21.

<sup>191</sup> World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (process development and manufacturing to support human trials of an AIDS vaccine would cost \$50 million.)

<sup>192</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 51.

<sup>193</sup> *Id.*; Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 4-5.

<sup>194</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 51.

<sup>195</sup> *Id.* at p. 51.

<sup>196</sup> *Id.* at p. 49.

<sup>197</sup> A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 92.

<sup>198</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 51.

<sup>199</sup> Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001).

<sup>200</sup> Lisa Jarvis, “Fine Chemicals Producers Need to Look Beyond Size,” *Chemical Market Reporter*, p. 8 (Oct. 22 2001).

<sup>201</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 48.

<sup>202</sup> *Id.* p. 49.

<sup>203</sup> Lisa Jarvis, “Fine Chemicals Producers Need to Look Beyond Size,” *Chemical Market Reporter*, p. 8 (Oct. 22 2001).

<sup>204</sup> PhRMA, *Profile: Pharmaceutical Industry* (2004), at p. 3.

<sup>205</sup> Global Alliance, *Economics of TB Drug*, *supra*, at p. 49.

<sup>206</sup> Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2 2003) p.17 (Quoting AspenTech estimate that outsourcing can cut R&D costs by 5%).

<sup>207</sup> Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001) (Mounting cost pressure and increasingly complex technologies have made pharmas more willing to outsource).

<sup>208</sup> Clay Boswell, “InnoCentive and Web-Based Collaborative Innovation,” *Chemical Market Reporter* (April 14, 2003).

<sup>209</sup> *Id.*

<sup>210</sup> Cynthia Challenger, “Smaller Fine Chemicals Players Find Their Niche,” *Chemical Market Reporter*, p. FR10 (Sept. 30 2002); *See also*, Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2 2003) p.17 (Contract producers are typically involved from Phase I; they also do preclinical work); Alex Scott, “Clariant Adds Capacity, Services; Moves Some Production to India,” *Chemical Week* p. 37 (Nov. 12, 2003) (Custom chemical manufacturers synthesize batches from five to two hundred kg. under either cGMP or non-cGMP conditions. They offer rapid synthesis of difficult compounds and support early phase synthesis up to and including Phase II trials); Alex Scott, “Custom Firms Focus on Cost-Cutting Efforts,” *Chemical Week* p. 63 (Sept. 24, 2003) (Contract suppliers can deliver one phase of a multistep synthesis or the entire compound. They can also re-design laboratory scale processes for pilot- and full-scale production); Alex Scott, “CSS Opens Early Phase Facility in UK,” *Chemical Week* (Sept. 10, 2003) (Custom chemical companies offer early phase intermediates, small scale cGMP manufacturing, and process development); Cynthia Challenger, “The Balancing Act of Small to Medium Sized Custom Manufacturers,” *Chemical Market Reporter* (April 14 2003) (company alliances offers pilot to large scale production facilities plus process development expertise); Cynthia Challenger, “The Balancing Act of Small to Medium Sized Custom Manufacturers,” *Chemical Market Reporter* (April 14 2003) (contract chemistry companies produce research compounds from gram to small kg scale.)

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<sup>211</sup> Cynthia Challenger, "Custom Manufacturing/Fine Chemicals: Views from the Trenches," *Chemical Market Reporter* (August 11, 2003); Robert Winder, "An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It," *Chemistry and Industry*, (June 2 2003) p.17 (contract process research); Alex Scott, "Custom Firms Focus on Cost-Cutting Efforts," *Chemical Week* p. 63 (Sept. 24, 2003).

<sup>212</sup> Cynthia Challenger, "Smaller Fine Chemicals Players Find Their Niche," *Chemical Market Reporter*, p. FR10 (Sept. 30 2002); Cynthia Challenger, "Custom Manufacturing/Fine Chemicals: Views from the Trenches," *Chemical Market Reporter* (August 11, 2003) (fine chemical suppliers network their capabilities "on a global basis"); Robert Winder, "An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It," *Chemistry and Industry*, (June 2 2003) p.17 (projects initially developed at one site can be moved to other alliance members when larger quantities are needed); Gordon Graff, "Custom Chemical Manufacturing," *Purchasing* (March 4, 2004), p. 24C3 (custom chemical companies are seeking manufacturing and development partners with expertise in small molecules and biotechnology).

<sup>213</sup> Cynthia Challenger, "Custom Manufacturing/Fine Chemicals: Views from the Trenches," *Chemical Market Reporter* (August 11, 2003) (Industry directories list 1200 companies in the pharmaceuticals, intermediate manufacturing, and allied industries. The largest ten suppliers have only 30 percent of the market).

<sup>214</sup> Cynthia Challenger, "The Balancing Act of Small to Medium Sized Custom Manufacturers," *Chemical Market Reporter* (April 14 2003) (large customers expect "almost annual price decreases" from custom manufacturing firms. They also expected added services without additional fees); cf. Office of Technology Assessment, *Pharmaceutical R&D, supra*, at Appendix G, pp. 302-3. (pressure to reduce costs is driving innovative processes in the custom manufacturing industry); Claudia Hume and Bill Schmitt, "Pharma's Prescription," *Chemical Week*, p. 21 (April 11 2001) (Pharma is no longer content to simply scale up a predetermined process or produce intermediates. It also wants technology expertise and process development, sometimes for minimal fees); *Id.* (In 1998, SmithKline Beecham told all of its preferred suppliers to add 20% value to their services through cost cuts, increased speed, or added services); *Id.* (fine chemical producers claim that competition has cut margins from 15-20% to 10-15%).

<sup>215</sup> Claudia Hume and Bill Schmitt, "Pharma's Prescription," *Chemical Week* p. 21 (April 11 2001).

<sup>216</sup> Robert Winder, "An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It," *Chemistry and Industry*, (June 2 2003) p.17; Cynthia Challenger, "Custom Manufacturing/Fine Chemicals: Views from the Trenches," *Chemical Market Reporter* (August 11, 2003).

<sup>217</sup> Claudia Hume and Bill Schmitt, "Pharma's Prescription," *Chemical Week* p. 21 (April 11 2001) (most pharma companies are inviting more bidders to compete for their outsourcing contracts. Novartis feels that heavy competition between suppliers is the best way to cut costs).

<sup>218</sup> *Id.* (competitive bids typically involve ten or more suppliers).

<sup>219</sup> Cynthia Challenger, "Custom Manufacturing/Fine Chemicals: Views from the Trenches," *Chemical Market Reporter* (August 11, 2003)

<sup>220</sup> *Id.* Challenger reports that large drugmakers are reducing the number of contract manufacturers with whom they work. Virtual pharmas typically use a single partner to take products from early-stage testing through launch. *Id.*

<sup>221</sup> *Id.*; Claudia Hume & Bill Schmidt, "Pharma's Prescription," *Chemical Week* (April 11, 2001) p. 21 (quoting Clariant executive: "I know of companies who at times sell below their production costs, just to keep their preferred supplier status").

<sup>222</sup> Claudia Hume and Bill Schmitt, "Pharma's Prescription," *Chemical Week* p. 21 (April 11 2001).

<sup>223</sup> Cynthia Challenger, "The Balancing Act of Small to Medium Sized Custom Manufacturers," *Chemical Market Reporter* (April 14 2003) (Large customers expect "almost annual price decreases" from custom manufacturing firms. They also expected added services without additional fees.)

<sup>224</sup> Kettler and White, "Valuing Industry Contributions," *supra*, at p. 4.

<sup>225</sup> Phil Norris, *Pharmaceutical Technology Europe*, p. 15 (March 1 2003) (small contract manufacturing organizations often deliver superior results).

<sup>226</sup> Claudia Hume and Bill Schmitt, "Pharma's Prescription," *Chemical Week* p. 21 (April 11 2001) (Pharma is no longer content to simply scale up a predetermined process or produce intermediates. It also wants technology expertise and process development, sometimes for minimal fees); *Id.* (In 1998, SmithKline Beecham told all of its preferred suppliers to add 20% value to their services through cost cuts, increased speed, or added services); *Id.* (fine chemical producers claim that competition has cut margins from 15-20% to 10-15%).

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<sup>227</sup> *Id.* (a few companies have refused to sign over rights. Pharmas will only agree if they have no other choice and cannot circumvent the patent); Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2 2003) p.17 (Dow performs development work on a fee-for-service basis, with all novel IP belonging to the customer). Some custom chemical makers also offer “shared risk models” in which they assume part of the development cost in exchange for “future opportunities and simplified pricing.” Cynthia Challenger, “The Balancing Act of Small to Medium Sized Custom Manufacturers,” *Chemical Market Reporter* (April 14 2003).

<sup>228</sup> Global Alliance, *Economics of TB Drug Development*, *supra*, at pp. 52, 54 & E-2; DiMasi *et al.*, “The Price of Innovation,” *supra*, pp. 162 (71.0% success probability), 165 (21.6 months); Mark B. McClellan, “View from the Iron Triangle,” in *The Milken Institute Review* 6:79-86 (2004); PhRMA, *Profile: Pharmaceutical Industry* (2004), at pp. 4 (clinical trials can take five years), 43 (PhRMA reports that member companies spent 4.8% of their R&D budgets on Phase I trials in 2002. The figure is almost certainly understated since 11.3% of PhRMA’s data was “uncategorized.”); A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at pp. 91-93 (PPP estimates); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 924 (70% transition probability).

<sup>229</sup> Steven Walker & Dan Popeo, “Trends,” in *The Milken Institute Review* 6:7 (2004); Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1.

<sup>230</sup> Office of Technology Assessment, *Pharmaceutical R&D*: *supra*, at p. 5.

<sup>231</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 155.

<sup>232</sup> *Id.* at p. 155; Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 5.

<sup>233</sup> Walker and Popeo, “Trends,” *supra*.

<sup>234</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 41 (Phase I tests must normally be performed in the environment and against strains of the disease where the drug will eventually be used); Global Forum for Health Research, *10/90 Report*, *supra*, at pp. 206-07 (NIH’s HIV Vaccine Trials Network was established in 1999 and operates a global network of 12 domestic and 12 foreign sites. It conducts Phase I, II, and III trials. Eight trials are currently underway), p. 208 (HIV Prevention Trials Network has conducted five Phase I/II trials to evaluate topical microbicides).

<sup>235</sup> Krishanu Saha, “Easing FDA’s Precarious Racial/Ethnicity Guidelines Can Advance Global Health” (May 2004) (unpublished; on file with the author); FDA, “Guidelines for Industry: Collection of Race and Ethnicity Data in Clinical Trials” (2003) (FDA and international regulatory standards limit drugmakers’ ability to conduct tests in areas where populations are genetically distinct or environments that are significantly different from the target group). Saha remarks that these effects are less important for complex, rapidly evolving infectious diseases. Neglected diseases frequently fit this description.

<sup>236</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 24.

<sup>237</sup> *Id.*

<sup>238</sup> Global Forum for Health Research, *10/90 Report*, *supra*, at p. 195. (private-public partnerships work with local governments to conduct studies where disease is endemic.)

<sup>239</sup> Spivey *et al.*, “The US FDA in the Drug Development,” *supra*, at pp. 704 (meetings are mandated by Section 119 of the FDA Modernization Act of 1997), 704 (meetings have come more common over the past decade and are designed to ensure that studies will be sufficient to meet their stated objectives), 717 (early and continuing discussions facilitate approval); Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices,” *supra*, (system transparency was probably improved by The Food and Drug Administration Modernization Act (1997), which gives companies the right to meet and discuss the design of clinical studies needed for FDA approval); Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 313 (NIH’s Cancer Therapy Evaluation Program has a Regulatory Affairs Branch that prepares and submits IND applications for human trials that lack a commercial sponsor).

<sup>240</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002).

<sup>241</sup> *Id.*

<sup>242</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 163 (company strategists often use Phase I trials to get an early look at whether a product is likely to fail. Phase I trials did a slightly better job of weeding out failures in the 1990s than they had in the 1970s. However, they also became larger, more complex, and costly in the process).

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<sup>243</sup> Alex Scott, "CSS Opens Early Phase Facility in UK," *Chemical Week* (Sept. 10, 2003).

<sup>244</sup> As of 1980, there were 12,000 clinical investigators (usually physicians) conducting trials in the US. Several clinical investigators grossed more than \$1 million per year. Between 1964 and 1982, FDA inquiries resulted in 45 clinical investigators being declared ineligible to receive investigational drugs. Several companies were also found guilty of selective reporting. FDA's Division of Scientific Investigations frequently finds that physicians do not adhere to protocols, maintain accurate case histories, or submit test reports. Alexander Kohn, *False Prophets* (Blackwell 1986) at pp. 176-77, 181-82; *see also*, William Broad & Nicholas Wade *Betrayers of the Truth* (Simon & Schuster, New York 1982) (FDA study showed that 16 of 50 audited physicians submitted false data).

<sup>245</sup> Scott Hensley, "Drug Prices – Why They Keep Soaring," *Wall Street Journal* (May 2, 2002) (Pfizer started a small Phase I study in late 1996. Despite a mysterious rash in one individual, the company went forward with a larger test involving 114 people a year later).

<sup>246</sup> *Id.* (after first Pfizer encountered an unexplained rash in a single patient, the company invested in a larger study to substantiate safety.)

<sup>247</sup> World Bank Task Force, "HIV Vaccine Industry Study," *supra*, (reporting "considerable skepticism" outside directly affected firms as to whether AIDS vaccines based on GP 120 and pox vector candidates would succeed in Phase II and Phase III trials.)

<sup>248</sup> DiMasi *et al.*, "The Price of Innovation," *supra*, at pp. 162, 165 (Phase II trials last 25.7 months, cost \$23.5m, and have a success rate of 31.4%); A. Towse *et al.*, "Estimates of the Medium Term Financial Resource Needs," *supra*, at pp. 91 - 92 (PPP estimates); PhRMA, *Profile: Pharmaceutical Industry* (2004), at p. 43 (member companies spent 9.6% of their R&D budgets on Phase II trials in 2002); Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 54 (arguing that Phase II trials could be conducted for \$3.4 million); World Bank Task Force, "HIV Vaccine Industry Study," *supra*, (consulting firm estimate: primate and clinical studies of a new AIDS vaccine through Phase II would take two years and cost \$15 million); Nwaka and Ridley, "Virtual Drug Discovery and Development for Neglected Diseases," *supra*, at 924 (50% transition probability).

<sup>249</sup> DiMasi *et al.*, "The Price of Innovation," *supra*, at p. 151 (Phase II tests are conducted on subjects who have the targeted disease or condition and are designed to obtain evidence on safety and preliminary efficacy data); Walker and Popeo, "Trends," *supra*, (Phase II trials enroll up to several hundred patients and take from one to several years to complete); Jeff Garth & Sheryl Gay Stolberg, "Drug Makers Reap Profits on Tax-Backed Research," *New York Times* (April 23, 2000), p. 1.1 (Phase II drugs involve 100-300 volunteer patients and focus on efficacy and side effects); Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 5 (Phase II trials examine compound's potential usefulness and short term risks).

<sup>250</sup> Walker and Popeo, "Trends," *supra*.

<sup>251</sup> *Id.*

<sup>252</sup> *Id.*

<sup>253</sup> Alex Scott, "CSS Opens Early Phase Facility in UK," *Chemical Week* (Sept. 10, 2003)

<sup>254</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 313 (NIH's Antiviral Research program supports Phase I and II studies; NIH's Cancer Therapy Evaluation Program has sponsored trials to determine the efficacy and toxicity of new drugs.), 314 (Walter Reed has capability to do clinical testing through collaborative agreements with public organizations (e.g. WHO) and private pharmaceutical firms who provide clinical testing and marketing of successful compounds).

<sup>255</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 41.

<sup>256</sup> Global Forum for Health Research, *10/90 Report*, *supra*, at pp. 196 - 197 (CDC supported Bayer moxifloacin Phase II trials; CDC Trials Consortium is conducting additional Phase II trials; CDC and Europe are building trials capacity; TB Alliance is standardizing 15 sites in Africa, Asia, and South America).

<sup>257</sup> Alex Scott, "CSS Opens Early Phase Facility in UK," *Chemical Week* (Sept. 10, 2003)

<sup>258</sup> Scott Hensley, "Drug Prices – Why They Keep Soaring," *Wall Street Journal* (May 2, 2002) (Pfizer's development team suggested a six month trial to explore whether a drug candidate was effective. But this would take months or even years. Pfizer's R&D chair urged them to reconsider and "go for a home run" by pursuing a longer and more expensive test. This took six months to design. They eventually proposed a two year study. Pfizer funded it in 350 patients, "much larger than usual for such an early stage." The company hedged its bet by including interim analyses at six and twelve months).

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<sup>259</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 181 (European and Australian government cost-containment programs have persuaded many companies to test new drugs against existing products instead of placebo).

<sup>260</sup> *Id.* at p. 162 (drugs approved between 1990 and 2001 had a mean cost of \$23.5 million but a standard deviation of \$22.1 million.)

<sup>261</sup> Alex Scott, “CSS Opens Early Phase Facility in UK,” *Chemical Week* (Sept. 10, 2003)

<sup>262</sup> Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) (Pfizer asked three senior analysts not connected with the project, including a statistician, to review early results and decide whether development should go forward).

<sup>263</sup> *Id.* (After Pfizer drug failed, some scientists argued that study group had been too healthy. Pfizer decided to do follow up testing on an earlier group of patients, although this was considered a long shot).

<sup>264</sup> Spivey *et al.*, “The US FDA in the Drug Development,” *supra*, at p. 708 (companies usually invest intense preparation in end-of-Phase II meeting).

<sup>265</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 91 - 2 (PPP comparisons; includes a transition probability outlier of 0.25); *See also*, Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at p. 924 (transition probability of 0.65); PhRMA, *Profile: Pharmaceutical Industry* (2004), p. 43. (Member companies spent 20.2% of their R&D budgets on Phase III trials in 2002. The figure is almost certainly understated since 11.3% of PhRMA’s data was “uncategorized”); Scott Hensley, “Drug Prices – Why They Keep Soaring,” *Wall Street Journal* (May 2, 2002) at pp. 162, 165 (Phase III trials last 30.5 months and have a mean cost of \$86.3 million); World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (fewer than one in two vaccines that enter Phase III testing result in applications to the FDA); *Id.* (consulting firm estimate for AIDS vaccine: Phase III trials in two separate populations would cost \$55 million, and take five years); *Id.* (In the late 1990s, surveys typically quote the cost of Phase III trials at about \$30 million); Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), at p. 1.1 (Phase III trials range from \$10,000 to \$20,000 per patient); Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 188 (The private company VaxGen spent \$130 million to take a previously abandoned AIDS vaccine through Phase III trials. NIH contributed an additional \$11 million, the Gates Foundation contributed \$2 million, and the CDC contributed services to support tests in Thailand).

<sup>266</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 5; DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 156 (“Phase III clinical trials involve hundreds to thousands of patients and can take several years. The trials are designed to firmly establish efficacy and to uncover infrequent side-effects”); Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (“Phase 3 trials involve 1,000 to 5,000 people and are typically the costliest. They look for all adverse reactions to long-term use”); Walker and Popeo, “Trends,” *supra*, (“The primary goal is to establish whether the new treatment is better than an already-approved treatment”); Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices and Returns in the Pharmaceutical Industry (1998),” *supra*, at Chapter 3, p. 5 (Phase III trials establish effectiveness, optimal dosage, possible side effects, and adverse reactions).

<sup>267</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 313, 314 (Walter Reed has capability to do clinical testing through collaborative agreements with public organizations (*e.g.* WHO) and private pharmaceutical firms who provide clinical testing and marketing of successful compounds).

<sup>268</sup> Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 188 (AIDSVAX vaccine trials).

<sup>269</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 181 (Cost-containment by governments encourages companies to test new drugs against existing products instead of placebo).

<sup>270</sup> *Id.* at p. 162 (Phase III trials for successful drugs had a mean cost of \$86.3 million but a standard deviation of \$60.6 million).

<sup>271</sup> Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (Total Phase I through Phase III costs for Xatalan were less than \$30 million. Xatalan’s Phase III tests were limited to 829 people and only lasted six months); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 32 (substantial savings could be achieved by moving some Phase III trials into post-approval, Phase IV studies); Office of Technology Assessment,

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*Pharmaceutical R&D*, *supra*, at p. 6 (some R&D is driven by regulatory requirements); Global Alliance, *Economics of TB Drug Development*, *supra*, at p. 60 (even though two Phase III studies are usually required, FDA guidelines suggest that a single study “might be sufficient for approval”). Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices,” *supra*, at Chapter 3, p. 5.

<sup>272</sup> Ridley, “Product Development,” *supra*, at p. 201.

<sup>273</sup> Sander and Widdus, “Emerging Landscape,” *supra*, at p. 109.

<sup>274</sup> The private company VaxGen spent \$130 million to take a previously abandoned AIDS vaccine through Phase III trials. NIH contributed an additional \$11 million, the Gates Foundation contributed \$2 million, and the CDC contributed services to support tests in Thailand. Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 188.

<sup>275</sup> VaxGen employed 100 people to conduct trials and hired another 800 people under contract. 12,000 volunteers were screened, of which 7,930 volunteers were selected. The project generated more than one million case report forms. Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 188; Alex Scott, “CSS Opens Early Phase Facility in UK,” *Chemical Week* (Sept. 10, 2003) (testing services are available under contract and appear to be competitively supplied.)

<sup>276</sup> The cost of approvals is based on PhRMA data, assuming that the average company applies for one new drug each year. PhRMA, *Profile: Pharmaceutical Industry* (2004), p. 43 (Member companies spent \$2.5 million on approvals in 2002.) The figure is consistent with anecdotal evidence about how large drugmakers staff approval process teams. Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11 2003), p. A.1 (big drugmakers typically assign 30 or more people for months to prepare an application; small companies may make do with a single employee and three hired experts). For time and risk data, *see* Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 712 (review usually takes ten months but companies can expedite the process for a fee); DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 165 (Approvals averaged 18.2 months for drugs approved between 1990 and 2001); A. Towse *et al.*, “Estimates of the Medium Term Financial Resource Needs,” *supra*, at p. 91 (PPP estimates); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at p. 924 (95% transition probability). Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 710-11.

<sup>277</sup> Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 710-11.

<sup>278</sup> Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11 2003), p. A.1 (big drugmakers typically assign 30 or more people for months to prepare an application; small companies may make do with a single employee and three hired experts).

<sup>279</sup> NIH’s Cancer Therapy Evaluation Program has a Regulatory Affairs Branch that helps drugmakers compile data and other information for NDAs. Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 313.

<sup>280</sup> *But see*, Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 922 (use of contract research organizations to assemble regulatory dossiers).

<sup>281</sup> Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003) (Industry representatives believe that a new FDA commissioner would “help fill” today’s depleted drug discovery pipeline.)

<sup>282</sup> *See, e.g.*, Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at pp. 710-11 (drugmakers must make strategic decisions between resolving open scientific questions and submitting so much information that FDA is forced to “reset the clock” for review).

<sup>283</sup> *Id.* at pp. 710-11 (Drug companies should try to strike a balance between annoying the FDA and detecting problems at the earliest possible moment), 713 (Companies put a premium on learning and catering to the individual preferences of whichever FDA employees are conducting the review).

<sup>284</sup> The study compared the “most experienced” companies in GAO’s sample to the “least experienced.” Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices,” *supra*, at Chapter 3, p. 10. The effect may be smaller now that FDA has begun holding pre-NDA meetings

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to discuss the volume and types of information required for a successful application. Spivey *et al.* “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 711.

<sup>285</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 88 (Biovirx Inc. announcement that it will pursue licensing for rotavirus vaccine previously sold in the US but later withdrawn); Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11 2003), p. A.1 Winslow describes three examples. The first example discusses how the Medicines Company won approval for a blood thinner that was dropped by Biogen. The second example describes how Scios, Inc. won FDA approval for a heart failure drug after a previous FDA denial prompted Bayer to drop out of a co-development deal. The final example is more ambiguous. After the FDA asked for additional testing, Glaxo dropped out of a co-development deal to develop the drug. Although the drug’s owner found a new partner to continue testing, the decision was at least partly based on information received from employees who had used to work for Glaxo.

<sup>286</sup> The importance of specialized information about regulation, science, and markets is displayed in the exotic strategies that drugmakers frequently invent when seeking approval for the second time. Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (drugmaker made strategic decision to obtain approval as “second-string” medicine but used aggressive marketing to make it the “gold standard”). Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11 2003), p. A.1 (describing tactical decision to limit request for approval so that it excluded young women for whom suspicious rash raised the largest concerns.)

<sup>287</sup> World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (incremental investment in manufacturing capacity to deliver HIV vaccine would be on the order of \$100 to \$150 million); Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11, 2001) (commercial production typically costs \$500 per kg).

<sup>288</sup> Phil Norris, “Virtual Pharma: Re-Examining the Impact on Business Performance,” *Pharmaceutical Technology Europe* (March 1, 2003) (reporting manufacturing cost estimates of 17-22% and R&D cost estimates of 15-20%).

<sup>289</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 30; World Bank Task Force, “HIV Vaccine Industry Study,” *supra*, (capacity must often be built before clinical trial results are known.)

<sup>290</sup> Alex Scott, “CSS Opens Early Phase Facility in UK,” *Chemical Week* (Sept. 10, 2003) (most large pharma companies outsource manufacturing. One company reports that it has about 100 customers, including 16 of the global top 20 pharma companies); Alex Scott, “Custom Firms Focus on Cost-Cutting Efforts,” *Chemical Week* p. 63 (Sept. 24, 2003) (About 10% of all pharma intermediates are outsourced and the figure is growing); Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003) (quoting DowPharma estimate that one-sixth of APIs about to go off-patent will be outsourced); *Id.* (Astra-Zeneca already outsources 45 - 55% of synthesis steps and the figure is expected to rise); Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001) (consultants predict that 70 - 80% of drug manufacturing will eventually be outsourced).

<sup>291</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at Appendix G, pp. 302-3; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 32 (“Shared manufacturing facilities are not a possibility for vaccines as current regulations essentially preclude multiple use factories for large scale production”).

<sup>292</sup> Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003)

<sup>293</sup> Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2, 2003) p.17.

<sup>294</sup> Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001) (outsourcing is much more likely once a drug has been launched or becomes a mature product); Robert Winder, “An Early Start: Dow, DSM, Dugussa, Helsinn and Clariant Are All At It,” *Chemistry and Industry*, (June 2, 2003) p.17 (large pharmaceutical customers tend to keep small molecule API manufacturing in-house); Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003) (Outsourcing makes even more sense for new drugs that have higher potency, are more complex, and are made in smaller quantities); Alex Scott,

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“Custom Firms Focus on Cost-Cutting Efforts,” *Chemical Week* p. 63 (Sept. 24, 2003) (Big Pharma is not interested in outsourcing complex APIs for new drugs but does outsource mature, bulk products); Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001) (When patents expire, manufacturing contracts often go to Asian companies); Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003) (Big Pharma often outsources early-stage intermediates but typically waits until a few years before patent expiry to outsource intermediates to Asia.)

<sup>295</sup> Claudia Hume and Bill Schmitt, “Pharma’s Prescription,” *Chemical Week* p. 21 (April 11 2001) (outsourcing will increase India and China adopt new patent laws and become credible producers of advanced and custom intermediates).

<sup>296</sup> Cynthia Challenger, “Custom Manufacturing/Fine Chemicals: Views from the Trenches,” *Chemical Market Reporter* (August 11, 2003) (large drugmakers use multiple sourcing to contain prices for raw materials and advanced intermediates.)

<sup>297</sup> DiMasi *et al.*, “The Price of Innovation,” *supra*, at p. 173 (out of pocket costs for approved drugs comprised 25% of all R&D expenditures or roughly \$140 million); *See also*, PhRMA, *Profile: Pharmaceutical Industry* (2004), p. 43 (member companies spent 12.4% of their R&D budgets on Phase IV in 2002. The figure is almost certainly understated.)

<sup>298</sup> Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 715; Jeff Garth & Sheryl Gay Stolberg, “Drug Makers Reap Profits on Tax-Backed Research,” *New York Times* (April 23, 2000), p. 1.1 (“Phase IV tests consist of post-market testing as companies report adverse reactions not present during trials. The FDA evaluates the reports for trends and implications”).

<sup>299</sup> Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra*, at p. 716.

<sup>300</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at pp. 5-6.

<sup>301</sup> *Id.* at p. 6.

<sup>302</sup> Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process,” *supra* at p. 714 (reported adverse events now exceed 250,000 per year).

<sup>303</sup> *Id.* at p. 715.

<sup>304</sup> Office of Technology Assessment, *Pharmaceutical R&D*, *supra*, at p. 315 (NIH’s AIDS Clinical Trials Program supports off-label studies and data analysis).

<sup>305</sup> Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices,” *supra*, at Chapter 3, p. 10.

<sup>306</sup> Lorne Bleriot, “Chasing the Bald Eagle,” *Pharmaceutical Technology Europe* (June 1, 2001) p. 65 (biotechs need partners less as they gain access to “cash, validation, and marketing”); Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11 2003), p. A.1 (new product launches cost about \$100 million).

<sup>307</sup> Ron Winslow, “Orphan Rescue: How Small Firms Sometimes Hit Big With Drug Discards,” *Wall Street Journal*, (Aug. 11, 2003), p. A.1; Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 3 (More than half of the biotech drugs approved in 2000 were co-developed or marketed by pharmaceutical companies).

<sup>308</sup> Phil Norris, *Pharmaceutical Technology Europe*, p. 15 (March 1 2003)

<sup>309</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 15 (quoting Trevor Jones, Association for British Pharmaceutical Industries).

<sup>310</sup> *Id.*

<sup>311</sup> Ridley, “Product Development,” *supra*, at p. 204; Anthony Taubman, “Public-Private Management of Intellectual Property for Public Health Outcomes in the Developing World: The Lessons of Access Conditions in Research and Development Agreements,” (Initiative on Public-Private Partnerships for Health 2004) at p. 20 (LDCs have much greater dependence on private markets for drug dissemination than most industrialized countries).

<sup>312</sup> Ridley, “Product Development,” *supra*, at pp. 198 - 99, 204 (commercial drugmakers’ failure to obtain sponsors’ approval of Coartem and Malarone). *See also*, AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 81 (UNICEF only purchases drugs that have been “preapproved” by the WHO).

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- <sup>313</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. ix; Sander and Widdus, “Emerging Landscape” *supra*, at p. 102; *Id.* at p. 8 (The Gates Foundation continues to devote a “major portion of its grant-making” to the PPP and drug portfolio models. Beneficiaries include IAVI, MMV, Sequella Global TB Vaccine Foundation, and Tuberculosis Diagnostic Initiative); Ridley, “Product Development,” *supra*, at p. 197 (The Gates is “by far” the largest supporter of PPPs, although the Rockefeller Foundation has also been instrumental in many partnerships).
- <sup>314</sup> Sander & Widdus, “Emerging Landscape,” *supra*, at p. 98.
- <sup>315</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. ix; Sander and Widdus, “Emerging Landscape” *supra*, at p. 102.
- <sup>316</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 2.
- <sup>317</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 23 (Virtual Pharma is only now entering into clinical trials. Actual evidence of effectiveness is still some time off); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. ix (PPPs are still experimental. Until products are delivered, “best practices” are hard to design); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 927 (PPPs “are still in their infancy and are themselves social experiments”).
- <sup>318</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 11.
- <sup>319</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 27 (PPPs may step in when companies decide that development risks outweigh potential commercial benefits.)
- <sup>320</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 113 (sample of 17 PPPs).
- <sup>321</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 9.
- <sup>322</sup> Donald Francis, “The Cost of Developing Vaccines: Case Study of VaxGen’s HIV Candidate Vaccine,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 188 (The private company VaxGen spent \$130 million to take a previously abandoned AIDS vaccine through Phase III trials. NIH contributed an additional \$11 million, the Gates Foundation contributed \$2 million, and the CDC contributed services to support tests in Thailand).
- <sup>323</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at pp. 20-21 (Global Alliance has licensed PA-824 from Chiron for an undisclosed but reportedly discounted amount. Global Alliance will fund and manage the remaining preclinical and clinical work needed to bring the drug to market. Chiron retains the right to sell the drug in rich nations if it reimburses Global Alliance for all past development expenses and assumes responsibility for further development).
- <sup>324</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 13; Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 24 (Some PPPs supply resources and an overall objective but leave R&D to industry).
- <sup>325</sup> *Id.* at p. 13.
- <sup>326</sup> *Id.* at p. 12; Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 13 (quoting Trevor Jones, Association for British Pharmaceutical Industries: “Pharma companies must do trials to developed nation standards”).
- <sup>327</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 13 (GSK refused to test a malaria product in pregnant women, despite global health community’s priority. MMV will have to conduct these trials on its own).
- <sup>328</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 88 (Wyeth withdrew its rotavirus vaccine in 1999. Biovirx Inc announced that it would pursue licensing in 2004).
- <sup>329</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at pp. 23-24 (PPPs act as project managers); Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 13 (PPPs exercise complete control over R&D direction and pricing); Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 6 (biotech companies see PPP contracts as a source of income and a strategy for advancing their own technologies).
- <sup>330</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 113 (sample of 17 PPPs).
- <sup>331</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 28.

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- <sup>332</sup> A. Towse, J. Mestre-Ferrandiz & O. Renowden, Estimates of the Medium Term Financial Resource Needs for Development of Pharmaceuticals to Combat ‘Neglected Diseases,’” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 94.
- <sup>333</sup> Sander and Widdus, “Emerging Landscape,” *supra*, at p. 114.
- <sup>334</sup> *Id.* at p. 114 (IAVI has 80 employees, including experts on all phases of drug development up to and including manufacturing).
- <sup>335</sup> *Id.* at p. 120.
- <sup>336</sup> A. Towse, J. Mestre-Ferrandiz & O. Renowden, Estimates of the Medium Term Financial Resource Needs for Development of Pharmaceuticals to Combat ‘Neglected Diseases,’” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 89.
- <sup>337</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 167.
- <sup>338</sup> *Id.* at p. 164.
- <sup>339</sup> *Id.* at p. 164.
- <sup>340</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 106 (PPPs concentrate on R&D steps between lead compound identification and clinical trials).
- <sup>341</sup> Ridley, “Product Development,” *supra*, at p. 202. Most PPPs claim to perform at least some basic research. For a survey, see Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 122-38.
- <sup>342</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 166.
- <sup>343</sup> *Id.* at p. 168.
- <sup>344</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 113 (sample of 17 PPPs).
- <sup>345</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 19.
- <sup>346</sup> *Id.* at p. 21.
- <sup>347</sup> *Id.* at p. 21.
- <sup>348</sup> *Id.* at p. 14.
- <sup>349</sup> *Id.* at p. 20.
- <sup>350</sup> *Id.* at p. 19.
- <sup>351</sup> *Id.* at p. 20; Hannah Kellter and Karen White, “Valuing Industry Contributions,” *supra*, at pp. 17-18 (Company agreed that it would sell vaccine at 10% above production cost if clinical trials succeeded).
- <sup>352</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 14.
- <sup>353</sup> *Id.* at p. 20.
- <sup>354</sup> *Id.* at p. 16.
- <sup>355</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 17 (International Partnership on Microbicides has signed an agreement with a private partner to adapt the oral AIDS drug TMC 120 into a microbicidal gel. IPM will receive a royalty-free license to develop, manufacture, and distribute in LDCs. The corporate partner will bear development costs through Phase II and serve as a scientific advisor thereafter).
- <sup>356</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 19.
- <sup>357</sup> *Id.* at p. 109.
- <sup>358</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 2.
- <sup>359</sup> *Id.* at pp. 14, 32, 109 (In-kind contributions range from less than \$500,000 to over \$20 million for IAVI and MMV. In-kind contributions are almost 25% of MMV’s total capital committed).
- <sup>360</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 7.
- <sup>361</sup> Ridley, “Product Development,” *supra*, at p. 201.
- <sup>362</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 16 (describing transaction in which medical equipment maker received data on AIDS patients that would have been hard to acquire).
- <sup>363</sup> *Id.* at p. 16 (right of first refusal on assays and results).
- <sup>364</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 33; Sander and Widdus, “Emerging Landscape” *supra*, at p. 99.
- <sup>365</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 99; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 33.
- <sup>366</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 33.
- <sup>367</sup> *Id.* at p. 37.
- <sup>368</sup> Taubman, “Public-Private Management of Intellectual Property,” *supra*, at p. 23.
- <sup>369</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 112.

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<sup>370</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 10

<sup>371</sup> Global Forum for Health Research, *10/90 Report, supra*, at p. 204; Sander and Widdus, “Emerging Landscape” *supra*, at pp. 2, 17, 114; Kettler and White, “Valuing Industry Contributions,” *supra*; *10/90 Report, supra*, at p. 5; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 60; Sander and Widdus, “Emerging Landscape” *supra*, at pp. 129.

<sup>372</sup> Global Forum for Health Research, *10/90 Report, supra*, at p. 203; Sander and Widdus, “Emerging Landscape” *supra*, at pp. 106, 109, 131.

<sup>373</sup> Global Forum for Health Research, *10/90 Report, supra*, at pp. 216, 219; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 7, 15-16, 60; Declan Butler, “Gates Steps Up War on Malaria With Donation of \$168 Million,” *Nature* 425:331 (2003); Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 13 (quoting Trevor Jones, Association for British Pharmaceutical Industries); Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 5; Sander and Widdus, “Emerging Landscape” *supra*, at pp. 106, 109, 133; AdvancedMarkets Working Group, *Making Markets for Vaccines, supra*, at p. 86.

<sup>374</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines, supra*, at pp. 26, 86; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 62; Declan Butler, “Gates Steps Up War on Malaria With Donation of \$168 Million,” *Nature* 425:331 (2003); Sander and Widdus, “Emerging Landscape” *supra*, at p. 134.

<sup>375</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 62; Global Forum for Health Research, *10/90 Report, supra*, at pp. 196, 198; The Global Alliance for TB Drug Development, *Economics of TB Drug Development*(2001), at pp. 82-83; Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 5; Sander and Widdus, “Emerging Landscape” *supra*, at p. 127.

<sup>376</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 18, 59; Sander and Widdus, “Emerging Landscape” *supra*, at p. 122.

<sup>377</sup> *Id.* at p. 59; DNDi, *DNDi Business Plan, supra*, at pp. 10-18, 21, 24; Sander and Widdus, “Emerging Landscape” *supra*, at p. 123.

<sup>378</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at pp. 4, 21-22; Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 19, 60; Sander and Widdus, “Emerging Landscape” *supra*, at p. 130.

<sup>379</sup> UK pharma consultant Phil Norris uses consulting studies and industry knowledge to put manufacturing costs at between 17 and 22% of revenue. Phil Norris, *Pharmaceutical Technology Europe*, p. 15 (March 1 2003); *accord*, Mark B. McClellan, “View from the Iron Triangle,” in *The Milken Institute Review* 6:79-86 (2004) (Manufacturing costs account for only 25-50% of the total fixed and variable costs of delivering a new medicine to consumers).

<sup>380</sup> National Institute for Health Care Management, “Changing Patterns of Pharmaceutical Innovation” (2002), p. 18 (“generic drugs cost an estimated 30 to 60% less than their brand name counterparts”), available at <http://www.nihcm.org/innovations.pdf>; *see also*, 1998 Congressional Budget Office Report, “How Increased Competition from Generic Drugs Has Affected Prices,” *supra*, (when fewer than 10 firms manufacture generics, retail prices fall to about 60% of brand name; otherwise, price “less than half” of brand name.) <http://www-1.gsb.columbia.edu/faculty/FLichtenberg/B8299-002/Competition%20from%20Generic%20Drugs.pdf>; Michelle Matthews, “Greater Access to Generic Drugs,” *FDA Consumer Magazine* (September 9, 2003) (“for an average brand name drug that costs \$72, the generic version costs \$17.”) available at [http://www.fda.gov/fdac/features/2003/503\\_drug.html](http://www.fda.gov/fdac/features/2003/503_drug.html); Aidan Hollis, “An Efficient Reward System for Pharmaceutical Innovation,” (preprint 2004) at 11 (drug prices decrease 50 to 80% on average following the introduction of generics); Office of Technology Assessment, *Pharmaceutical R&D, supra*, at p. 305 (generic drugs in the 1980s cost 32% as much as pioneers); Lawton Burns & Patricia Danzon, “Drug Distribution: Putting the Pieces Together,” in *The Milken Institute Review* 6:61-70 (2004) (reporting that generics accounted for 45% of all drug units sold but 19% of revenues. The statement implies that the average generic price was 28% of the average patented price); Congressional Budget Office, “How Increased Competition from Generic Drugs has Affected Prices,” *supra*, at Chapter 3, pp. 21-22 (1994 data: When one to ten firms are producing generics, the generic price was 61% of the name brand price. When more than ten manufacturers enter the market, the average generic price falls to 0.42 – 0.46%. When more than 20 manufacturers enter the market, the average generic price was 39% of the name brand price); Peter Landers & Joanne S. Lublin, “Under a Microscope: Merck’s Big Bet on Research By Its

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Scientists Comes Up Short.” *Wall Street Journal* (Nov. 28, 2003), p. A.1 (generic versions of Claritin cost roughly 10% as much). Since FDA approval requires a non-trivial R&D investment, generic drugs provide only an upper limit on manufacturing costs.

<sup>381</sup> Ganslandt *et al.*, “The DEFEND Proposal,” at pp. 2-3 (TB is curable with drugs costing \$10-15 per patient); *Id.* at pp. 2-3 (Indian drug manufacturers Cipla and Hetero Drugs, Ltd. reportedly sell AIDS drugs below Merck’s price); Anon., “Price War Breaks Out Over AIDS Drugs in Africa as Generics Present Challenge,” *Wall Street Journal* (March 7, 2001) (Merck & Co. reduced two AIDS controlling drugs in Africa by 40-50%, adding to sharp price cuts previously announced the year before); F. Desmond McCarthy, Holger Wolf & Yi Wu, “The Burden of Malaria,” in *The Milken Institute Review* 6:54-60 (2004) (Current antimalarials cost \$1 to \$5 per bout of the disease); Kremer & Glennerster, *Strong Medicine, supra*, at p. 22 (A one week course of treatment for pneumonia costs less than 25 cents).

<sup>382</sup> Vaccines are routinely sold at between ten cents and one dollar per dose. Kremer & Glennerster, *Strong Medicine, supra*, at p. 41 (off-patent EPI vaccines run about 50 cents per dose); Farlow, “Analysis,” *supra*, at p. 17 (Kremer assumes competition and sets the manufacturing cost of a vaccine at 40-50 cents); J. Sachs, M. Kremer, A. Hamoudi, “The Case for a Vaccine Purchase Fund,” (Draft: 2001) at p. 6 (five vaccines distributed under the Expanded Program on Immunization cost \$1 per dose); World Bank Task Force, “HIV Vaccine Industry Study,” (current vaccines cost \$0.10 per dose); Gargee Ghosh, “Emerging Lessons in Preparing for Uptake of New Vaccines,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 181 (Hepatitis B vaccine cost \$15 - 30 in 1987. By 1991, Korean Green Cross was supplying it at 65 cents per dose); *Id.* (Merck and SmithKline Beecham introduced recombinant DNA vaccine in the late 1980s at \$40 per dose. Competition with LDC firms drove prices to just over \$1 per dose by the early 1990s. By 1997, Hep B vaccine was 30 cents per dose).

<sup>383</sup> WHO/Drug Action Program, “Selected Topics in Health Reform and Drug Financing” (1998) at p. 5; available at <http://www.who.int/medicines/library/dap/who-dap-98-3/who-dap-98-3.pdf>. In the US, drug purchases account for just ten percent of all healthcare spending. PhRMA, *Pharmaceutical Industry Profile: 2004* (2004) at p. 15.

<sup>384</sup> Cross-country comparisons suggest that health care spending is much more variable as a percentage of GDP than drug spending alone. WHO/Drug Action Program, “Selected Topics,” *supra* at p. 5.

<sup>385</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 17 (quoting Trevor Jones, Association for British Pharmaceutical Industries: Corruption is a major contributor to high prices paid by African patients).

<sup>386</sup> Kremer & Glennerster, *Strong Medicine, supra*, at 41 (A hepatitis B vaccine introduced at \$30 per dose is rarely used in low-income countries. Even at a dollar or two per dose, it still does not reach most children in the poorest countries); Farlow, “Analysis,” *supra*, at p. 16 (Yellow fever vaccine costs as little as four cents per shot to manufacture yet millions of children do not receive it); *see also*, Kremer & Glennerster draft manuscript at p. 10 (reducing AIDS drug prices to a few hundred dollars per dose allowed about 50,000 Africans use them; 4.1 million still cannot afford them).

<sup>387</sup> Quoted in David M. Kennedy, *Freedom from Fear: The American People in Depression and War, 1929-1945* (Oxford University Press: 1999) at p. 104

<sup>388</sup> The UK made its announcement in 1996. Wyeth Lederle licensed the first vaccine in October 1999 and received a contract for 10 million doses. Chiron (5 million doses) and Baxter (3 million doses) followed one year later. The initial price was \$21 per dose but fell below \$18 in later years. Kremer & Glennerster, *Strong Medicine, supra*, at pp. 58 - 59; AdvancedMarkets Working Group, *Making Markets for Vaccines, supra*, at p. 29.

<sup>389</sup> *Id.* at p. 30. A similar experiment is now underway in the US, where the Bioshield statute established a \$6 billion fund to purchase vaccines against biological weapons. The current statute consists of an appropriation to buy new drugs delivered within the next five years, but does not guarantee any particular price. Congress is currently considering “Bioshield 2” legislation that may include such guarantees.

<sup>390</sup> Companies disagree over whether the market offers adequate incentives for developing a safe and effective HIV vaccine. During the 1990s, the perceived minimum performance characteristics of an “acceptable” vaccine became significantly higher. Emotional and moral arguments suggest that a vaccine might never be approved. World Bank Task Force, “HIV Vaccine Industry Study,” *supra*.

<sup>391</sup> Ridley, “Product Development,” *supra*, at p. 200. Ridley does remark that spending increases have encouraged drugmakers to invest more in manufacturing and “improved formulations.” *See also*,

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AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 31 (increased budgets at GAVI and the Vaccine Fund have encouraged more firms to bid on contracts for existing vaccines.)

<sup>392</sup> *Id.* at p. 91. AdvancedMarkets has suggested that it might sometimes commit to purchasing a minimum quantity when negotiating contracts for late-stage products. LDCs could fund their co-payments from any source including general revenues, foreign aid, or NGOs.

<sup>393</sup> *Id.* at p. 94.

<sup>394</sup> *Id.* at p. 52.

<sup>395</sup> *Id.*

<sup>396</sup> *Id.* at p. 132.

<sup>397</sup> *Id.*

<sup>398</sup> *Id.* at p. 53.

<sup>399</sup> *Id.* at p. 46.

<sup>400</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at pp. 103-105.

<sup>401</sup> *Id.* at pp. 106-07 (arguing that it might be desirable to include clawback provision for firms that received push financing).

<sup>402</sup> *Id.* at p. 102 (arguing that IAC should be able to split payments between first and follow-on vaccines depending on extent to which second vaccine built on and improved first-generation product).

<sup>403</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 49 (if a superior product became available, countries could buy it.) In practice, the AdvancedMarkets proposal is slightly more complicated. First, the IAC could terminate sponsors' payment obligations if the disease burden fell by some substantial fraction tentatively set at between 50 or 75 percent. *Id.* at p. 47. The decision would be subject to a supermajority and/or subsequent legal challenges. Second, drugmakers would receive a guaranteed minimum payment even if their products arrived too late to share in the fund. This additional increment would be paid by relaxing the requirement that drugs that arrived after the first 200 million doses were purchased by sold on a cost-plus basis. *Id.* at 131.

<sup>404</sup> Farlow, "Analysis," *supra*, at pp. 55-56.

<sup>405</sup> *Id.* at p. 45.

<sup>406</sup> *Id.* at p. 66.

<sup>407</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 80.

<sup>408</sup> Ganslandt *et al.*, "The DEFEND Proposal," *supra*, at pp. 18-19 (companies would retain patent rights for non-participating countries.). Ganslandt *et al.* estimate that licenses for Sub-Saharan AIDS drugs would cost between \$500 million and \$1 billion per year. *Id.* at pp. 20 - 21. Adding subsidies needed to keep treatment below 40% GDP *per capita* would increase the cost to \$8 billion. *Id.*

<sup>409</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at pp. 80 (minimum program size for a reward system should be large, since frequent small payouts build confidence), 109 (program may have to be spread out over time so that initial work on "easy diseases" builds confidence for more ambitious projects.)

<sup>410</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 38.

<sup>411</sup> *Id.* at p. 52.

<sup>412</sup> *Id.* at p. 129.

<sup>413</sup> Aidan Hollis, "An Efficient Reward System for Pharmaceutical Innovation," (preprint 2004) at 2, 17 (noting that QALYs suffer from "difficulties relating to the quality of assessments, shortages of qualified staff, off-label use of drugs, and biased studies").

<sup>414</sup> James K. Hammitt, "How Much is a QALY Worth? Admissible Utility Functions for Health and Wealth," (May 2002), available at <http://www.huebnergeneva.org/documents/hammitt.pdf#search='hammitt%20and%20qaly'>.

<sup>415</sup> Maurice McGregor, "Cost-Utility Analysis: Use QALYs Only With Great Caution," *Canadian Medical Association Journal* **168**:433 (2003).

<sup>416</sup> Ceri Phillips and Guy Thompson, "What is A QALY?," available at [www.evidence-based-medicine.co.uk](http://www.evidence-based-medicine.co.uk).

<sup>417</sup> Mo Malek, "Implementing QALYs," available at [www.evidence-based-medicine.co.uk](http://www.evidence-based-medicine.co.uk); *cf.* Maurice McGregor, "Cost-Utility Analysis," *supra*.

<sup>418</sup> Respectable estimates of malaria are highly uncertain. AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 24 ("possibly as many as two million."); *see, e.g.*, Anon., "Parasitology and Neglected Diseases," ("~ 3 million deaths/yr") available at [http://www.library.csi.cuny.edu/~davis/faculty\\_page/Parasit lnks/parasitology links.html](http://www.library.csi.cuny.edu/~davis/faculty_page/Parasit lnks/parasitology links.html).

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- <sup>419</sup> Maurice McGregor, "Cost-Utility Analysis," *supra*.
- <sup>420</sup> See, e.g., Maurer & Scotchmer, "Procuring Knowledge," *supra*, at p. 11; Aidan Hollis, "An Efficient Reward System for Pharmaceutical Innovation," (preprint 2004)
- <sup>421</sup> French aviation prizes in the early Twentieth Century *split* prizes among the number of entrants who accomplished the goal by a set date. Paul Hoffman, *Wings of Madness: Alberto Santos-Dumont and the Invention of Flight*, (New York: Thea: 2003), pp. 83-84 (offering shared prize for entrants who flew around the Eiffel Tower by a date certain. The money was "divided in proportion to their respective times."); Cf., Farlow, "Analysis," *supra*, at p. 55 (winner-take-all system may reduce the total number of competing development efforts).
- <sup>422</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 133.
- <sup>423</sup> See, e.g., Paul Hoffman, *Wings of Madness*, *supra*, at pp. 83-84 (offering shared prize for entrants who flew around the Eiffel Tower by a date certain. The money was "divided in proportion to their respective times.")
- <sup>424</sup> World Bank Task Force, "HIV Vaccine Industry Study," *supra* (industry is skeptical of prizes because of (a) their winner-take-all quality, and (b) the lack of any guarantee that winning entries will actually be manufactured or purchased).
- <sup>425</sup> Defense Advanced Research Projects Agency, "DARPA Grand Challenge," available at <http://www.darpa.mil/grandchallenge/>.
- <sup>426</sup> NASA, "Overview and Goals for Centennial Challenges," [http://www.centennialchallenges.nasa.gov/cc\\_overview.pdf](http://www.centennialchallenges.nasa.gov/cc_overview.pdf)
- <sup>427</sup> Marc Hunter, "Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies," (Initiative on Public-Private Partnerships for Health 2004) at p. 6.
- <sup>428</sup> Kremer & Glennerster, *Strong Medicine*, *supra* at pp. 72-73. Kremer refers to the latter as "best entry tournaments."
- <sup>429</sup> Clay Boswell, "InnoCentive and Web-Based Collaborative Innovation," *Chemical Market Reporter* (April 14, 2003). As of 2003, InnoCentive had paid out approximately twenty awards with an aggregate value of \$500,000.
- <sup>430</sup> Dean Baker, "Financing Drug Research: What Are the Issues?" (2004 ), p. 18, available at [www.cepr.net](http://www.cepr.net) (arguing that rewards for ideas should seldom exceed \$10 million).
- <sup>431</sup> Nwaka and Widdus, "The Current Research-to-Development 'Hand-Off'" *supra*, at p. 164.
- <sup>432</sup> *Id.*
- <sup>433</sup> The Salk and Sabin polio vaccines were both developed without patent protection of any kind. Six manufacturers agreed to produce the vaccine at cost. In addition to contract revenue, each company received a lead-time advantage over competitors once the vaccine entered full-scale production. Smith, Jane S., *Patenting the Sun: Polio and the Salk Vaccine* (New York : Anchor/Doubleday, 1991) at pp 221-22, 246-49.
- <sup>434</sup> The US Department of Health and Human Services has recently agreed to purchase two million doses of bird flu vaccine for use in Phase I trials. The vaccine will be discarded if tests are unsuccessful. Anon., "US Orders Bird Flu Vaccine Before Start of Clinical Trials" *Nature* **421**:498 (2004).
- <sup>435</sup> Dean Baker, "Financing Drug Research: What Are the Issues?" (2004 ), at pp. 16 - 17, available at [www.cepr.net](http://www.cepr.net). Kucinich chose the \$25 billion figure to match estimates of worldwide drug research under the patent system.
- <sup>436</sup> S. Maurer, A. Rai, & A. Sali, "Finding Cures For Tropical Diseases: Is Open Source an Answer?" *PLOS: Medicine* **1**:156 (2004), available at <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0010056>
- <sup>437</sup> Farlow, "Analysis," *supra*, at p. 34.
- <sup>438</sup> D. Normile, "Syngenta Agrees to Wider Release," *Science*, **296**:1785 (2002); D. Butler, "Geneticists Get Steamed UP Over Public Access to Rice Genome," *Nature* **416**:111 (2002); D. Butler, "Rice Genome Sequencers Cook Up Merger," *Nature* **416**:573 (2002); N. Wade, "Experts Say They Have Key to Rice Genes," *The New York Times* (April 5, 2002); D. Butler & P. Pockeley, ". . . As Monsanto Makes Rice Genome Public," *Nature* **414**:534 (2000); D. Normile, "Monsanto Donates Its Share of Golden Rice," *Science* **289**:843 (2000); E. Penisi, "Stealth Genome Rocks Rice Researchers," *Science* **288**:239 (2000).
- <sup>439</sup> Sarah Houlton, "Drugs for Neglected Diseases: A Non-Profit Partnership Will Create a Structure to Develop Therapies That are Badly Needed in Poor Countries," *Pharmaceutical Executive*, (Aug. 1, 2003) p. 28.

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- <sup>440</sup> Russ Altman, (Stanford University) personal communication.
- <sup>441</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 23 (“One company, for example, expressed a willingness to allow scientists or PPPs access to their libraries of ‘safe compounds.’”).
- <sup>442</sup> Maurer *et al.*, “Finding Cures for Tropical Diseases,” *supra*.
- <sup>443</sup> Y. Benkler, “Commons Based Strategies and the Problems of Patents,” *Science* **305**:1110 (2004).
- <sup>444</sup> Microsoft Corporation, “Shared Source Initiative Home Page,” <http://www.microsoft.com/resources/sharedsource/default.mspx>.
- <sup>445</sup> E. Von Hippel (MIT) (personal communication). Von Hippel’s ideas are described at K. Cukier “An Open Source Shot in the Arm?,” *The Economist* (June 10, 2004), available at [http://www.economist.com/science/tq/displayStory.cfm?story\\_id=2724420](http://www.economist.com/science/tq/displayStory.cfm?story_id=2724420).
- <sup>446</sup> DNDi, *DNDi Business Plan*, *supra*, at p. 10.
- <sup>447</sup> See, e.g., William Broad and Nicholas Wade, *Betrayers of the Truth*, (Simon & Schuster, New York 1982) at pp. 81 - 83 (FDA audits showed that sixteen out of fifty physicians submitted false data); Alexander Kohn, *False Prophets* (Blackwell 1986), pp. 181-83 (FDA investigation revealed that physicians failed to follow protocols, maintain accurate case histories, or submit test reports. In some cases, physicians reported results for patients who received no drugs at all.)
- <sup>448</sup> Gmap.net Home Page, available at [www.gMap.net](http://www.gMap.net). See also, Gmap.net, “Research Partnership,” available at <http://www.gmap.net/intro4.htm>.
- <sup>449</sup> See, e.g., Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 25 (asking whether additional grant funding would persuade academics to spend more time translating results into lead compounds); Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 64 (expressing doubt that academics are willing to perform non-prestigious tasks like holding clinical trials or developing animal models for disease.)
- <sup>450</sup> Alison Abbott, “Into Unknown Territory,” *Nature* **420**:600 (2002); AfCS, “The Signaling Gateway,” at <http://www.signaling-gateway.org/>.
- <sup>451</sup> See, e.g., US State Department, “Fact Sheet: US Global Vaccine Enterprise” (2004), available at [usinfo.state.gov/gi/Archive/2004/Jun/14-442142.html](http://usinfo.state.gov/gi/Archive/2004/Jun/14-442142.html); see also, Richard D. Klausner *et al.*, “The Need for a Global HIV Vaccine Enterprise,” *Science* **300**:2036 (2003).
- <sup>452</sup> Richard D. Klausner, *supra*, at pp. 2037 – 39.
- <sup>453</sup> Klausner *et al.* argue that the number of individual centers would be set by the number of “agreed-on ‘cells’ of the vaccine product pipeline grid.” *Id.* at 2037. Apparently, project leaders would identify and agree on “cells” through informal discussion without using formal incentives to elicit information. If ideas are widely-diffused across the globe, it might make more sense to use mechanisms like patents, prizes, or grants.
- <sup>454</sup> For further details, see Copyright Society of the USA, “Music: Frequently Asked Questions,” available at <http://www.csusa.org/face/music/faqs.htm#foxlicense>.
- <sup>455</sup> Tracy Lewis & J.H. Reichman, “Using Liability Rules to Simulate Local Innovation in Developing Countries: A Law and Economics Primer” (Draft: April 2003).
- <sup>456</sup> N. Covert, “Cutting Edge: A History of Fort Detrick” (2000), available at [http://www.detrick.army.mil/detrick/cutting\\_edge/index.cfm?chapter12](http://www.detrick.army.mil/detrick/cutting_edge/index.cfm?chapter12)
- <sup>457</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 24 (PPP’s can ask retired commercial scientists and clinicians to work as volunteers or under contract); *Id.* at p. 15 (IOWH is staffed with pharmaceutical scientists with international drug development and regulatory experience. Advisory boards include representatives from GSK, Aventis, Pfizer, Astra-Zeneca, and Merck); Sander and Widdus, “Emerging Landscape” *supra*, at pp. 113 (PPP’s hire individuals with strong product development track records). Many PPP’s draw a large fraction of their executives from industry. Examples include DNDi (50%), Global Alliance (50%), IAVI (73%), iOWH (75%), IPM (50%), MMV (100%), and MVI (40%). *Id.* at 122-138.
- <sup>458</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 115 (quoting PPP executive: “You have not really learned about portfolio management until you have had to drop a favored candidate from your list”).
- <sup>459</sup> Sander and Widdus, “Emerging Landscape” *supra*, at pp. 114, 115 (looking at which candidates have been dropped, and when, is an important check for making sure that management is effective); Marc Pfitzer, “Demonstrating Value: Performance Metrics for Health Product Development Private-Public Partnerships,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 160 (PPP’s have a good sense of how many compounds will have to be screened and can demonstrate when

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projects are transitioned based on best practices. “These measures can quickly point to deviations.”); *Id.* at 161 (rate of meeting milestones demonstrates ability to reach objectives).

<sup>460</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 28; *see also*, Nwaka and Ridley, p. 921 (pharmaceutical companies hire outside consultants to audit portfolio decisions).

<sup>461</sup> Marc Pfitzer, “Demonstrating Value: Performance Metrics for Health Product Development Private-Public Partnerships,” in Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 162.

<sup>462</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 29.

<sup>463</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 105 (eight of seventeen sampled PPPs were hosted by a larger organization).

<sup>464</sup> Kremer & Glennerster, *Strong Medicine*, *supra*, at p. 63; Kremer, “*Making Vaccines Pay*,” *supra*.

<sup>465</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 101; *but see*, Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 12 (arguing that MMV/GSK is the “only exception” to statement that “[i]ndustry contributions to PPPs have largely been restricted to well-defined deals on specific projects”); Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 926 (arguing that long-term PPP/company relationships would bring “stability to project management”).

<sup>466</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 119.

<sup>467</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 25.

<sup>468</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 2 and 32 (PPP should share expensive, late-stage R&D projects like clinical trials and building manufacturing capacity); 37 (Groups should coordinate on establishing capacity, coordinating the sequence and timing of trials, and adopting common systems); Sander and Widdus, “Emerging Landscape” *supra*, at p. 119 (PPP should coordinate by sharing more platforms).

<sup>469</sup> Nwaka and Ridley, “Virtual Drug Discovery and Development for Neglected Diseases,” *supra*, at 926.

<sup>470</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 30.

<sup>471</sup> *Id.* at p. 30 (industry partners respect PPPs with “strong bank balances”).

<sup>472</sup> Ridley, “Product Development,” *supra*, at p. 200.

<sup>473</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at pp. 12, 14 (“If fewer potential collaborators can be found to take on the necessary work, a [PPP] will need to have a proportionally larger staff to manage or conduct activities ‘in-house’”); Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 13 (“Even assuming that PPPs can identify relatively inexpensive contract researchers and manufacturing partners in the developing world (a talent still to be tested), they will need to pay for additional staff to manage and monitor the project.”).

<sup>474</sup> Sander and Widdus, “Emerging Landscape” *supra*, at p. 114.

<sup>475</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 12 (arguing that neglected fields, novel classes of products, and vaccines are likely to have small numbers of potential collaborators.)

<sup>476</sup> *Id.* at p. 14.

<sup>477</sup> Nwaka and Widdus, “The Current Research-to-Development ‘Hand-Off’” *supra*, at p. 164.

<sup>478</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 25 (recent license by Yale University authorizing commercial development of compound as athlete’s foot remedy but reserving possible applications to Chagas diseases).

<sup>479</sup> Tim Hubbard and James Love, “A New Trade Framework for Global Healthcare R&D,” *PloS Biology* 2:0147 (2004).

<sup>480</sup> AdvancedMarkets Working Group, *Making Markets for Vaccines*, *supra*, at p. 81.

<sup>481</sup> Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 24

<sup>482</sup> *See, e.g.*, Spivey *et al.*, “The US FDA in the Drug Development, Evaluation and Approval Process” *supra*, at p. 711 (arguing that FDA’s animal toxicity data requirements are excessive and ought to be discarded). Current FDA practice is significantly more elaborate than comparable procedures in Europe, Japan, or the US itself prior to 1962. *Id.*

<sup>483</sup> World Bank Task Force, “HIV Vaccine Industry Study,” *supra*. (minimum standard for an acceptable AIDS vaccine is higher in rich nations because of (a) stable and limited infectivity found in rich nations, and (b) the ability of rich nations to support aggressive combination therapies for those who are infected); Widdus and White, “Combating Diseases Associated With Poverty,” *supra*, at p. 26 (FDA risk-benefit thresholds may be inappropriate for LDCs).

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<sup>484</sup> Marc Hunter, “Partnerships for Developing World Health: Decision and Management Issues for Pharmaceutical Companies,” (Initiative on Public-Private Partnerships for Health 2004) at p. 13 (quoting Robert Ridley).

<sup>485</sup> Kettler and White, “Valuing Industry Contributions,” *supra*, at p. 11 (low commercial investment means that PPPs cannot realistically threaten to break off negotiations with private partners in favor of some other product).

<sup>486</sup> S. Maurer, “Promoting and Disseminating Knowledge: The Public/Private Interface,” (National Academy of Sciences 2002) at pp. 55-56 (defensive publishing of expressed sequence tags and “SNPs”), available at [http://www7.nationalacademies.org/biso/PD\\_Maurer\\_pdf.pdf](http://www7.nationalacademies.org/biso/PD_Maurer_pdf.pdf) .