International Conference on Pharmaceutical Innovation
Taipei, Republic of China
May 27, 2005

WHEN PATENTS FAIL: FINDING NEW DRUGS FOR THE DEVELOPING WORLD[*]

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[*] The author thanks Charles Clift, Andrew Farlow, Bronwyn Hall, Aiden Hollis, Victoria Hale, Jean Lanjouw, Donald Light, Solomon Nwaka, Owen Barder, Arti Rai, Andrej Sali, and Suzanne Scotchmer for helpful discussions.

Abstract

Worldwide drug research budgets for diseases of poverty (*e.g.* malaria, African sleeping sickness) will likely double by 2010. The question is how best to spend this money. This paper analyzes the possible strategies in terms of two new categories. End-to-End ("E2E") proposals try to mimic the patent system by using a single reward to elicit innovation throughout the entire drug discovery pipeline. However, E2E strategies have generic drawbacks. Because sponsors have very little information about the rewards needed to elicit R&D, they are likely to overpay by twenty to thirty percent on average. Companies may also demand extra compensation to cover the risk that sponsors will renege over the very long periods (12 – 15 years) needed to develop new drugs. Pay-as-You-Go ("PaYG") strategies avoid these penalties by dividing incentives into small incremental rewards that are paid out at multiple points along the drug discovery pipeline. Sponsors are likely to find PaYG schemes less expensive than E2E strategies unless commercial pharmaceutical companies are substantially better at "picking winners" than non-profit entities.

I. Introduction

Rich nations use patent incentives to fund most new drug discovery. Scholars and politicians vehemently disagree about whether this policy is, in general, correct. However, there is no question that patent incentives have failed for developing world diseases like malaria and sleeping sickness. Collectively, these "diseases of poverty" afflict one-tenth of the earth's population. However, current patent incentives do very little to create drugs for these diseases. Of the 1,233 drugs licensed worldwide between 1975 and 1997, only four were specifically developed by commercial pharmaceutical companies to treat tropical diseases in humans. [1] Given that patents have not worked, what incentives should replace them?

The question is becoming urgent. After decades of neglect, worldwide R&D spending on diseases of poverty could reach $500 million per year by decade's end. [2] Though substantial, this sum is hardly overwhelming compared to the multibillion dollar R&D budgets of most large pharmaceutical companies. In what follows we assume that success is possible if – but only if – sponsors practice rigid cost containment.

Section II ("Current Proposals") introduces the various incentive systems that have been suggested for promoting R&D for diseases of poverty. These can conveniently be divided into End-to-End ("E2E") strategies in which governments and non-profits (collectively, "sponsors") offer a single large reward when a new drug is finally delivered and Pay-as-You-Go ("PaYG") proposals in which sponsors offer smaller but more frequent rewards at multiple stages along the drug discovery pipeline. Section III ("End-to-End Strategies") examines the generic strengths and weaknesses of E2E strategies. Section IV ("Pay-as-You-Go Strategies") provides a similar analysis for PaYG systems. It also comments on the incentives that PaYG sponsors are likely to choose at each stage of the drug discovery pipeline. Section V ("Mixed Strategies") describes the benefits and drawbacks of designing hybrid proposals that combine E2E, PaYG, and/or conventional patent incentives within a single strategy. Section VII presents a brief conclusion.

II Current Proposals

Current proposals can be conveniently divided into three categories. First, End-to-End ("E2E") strategies try to mimic the patent system by establishing a single reward for researchers who successfully complete the entire drug discovery process. The most discussed E2E proposals are Advanced Purchase Commitments ("APCs") in which governments and non-profits (collectively, "sponsors") promise to pay a set price for new drugs that meet some minimum standard. Other E2E schemes are based on prizes. For example, Hollis [3] has proposed paying prizes to companies that produce new drugs based on a mathematical formula ("QALYs") that quantifies therapeutic benefit. Although Hollis concedes that the QALY formula is an imperfect measure of social value, he argues that conventional pharmaceutical markets are even worse. Perhaps the simplest E2E scheme is for sponsors to increase their current and/or projected purchasing

budgets for pharmaceuticals, thereby encouraging companies to develop new products. Almost any form of increased spending satisfies this model.[*]

Pay-as-You-Go ("PaYG") schemes are fundamentally different because they place substantial decision-making responsibilities in the hands of non-profit managers. The basic idea is to create the non-profit equivalent of a pharmaceutical company. In practice, this means hiring a drug management team to identify promising compounds, prioritize needed R&D, and pay outside entities to perform further research. Private-Public Partnerships ("PPPs") like the Institute for One World Health, the Drugs for Neglected Diseases Initiative, and The Medicines for Malaria Venture currently host highly professional teams that manage large drug candidate portfolios. Their reliance on outside partners to provide R&D services mimics the extensive outsourcing practiced by most modern pharmaceutical companies.

Finally, many commentators argue that E2E and PaYG should be combined with each other and/or conventional patent incentives within a single strategy. PPPs routinely experiment with schemes that subsidize commercial R&D programs in cases where conventional patent incentives are thought to be inadequate.

III. End-to-End Strategies

Drug discovery is a pipeline composed of roughly one dozen separate and distinct R&D steps. If governments and non-profits (collectively "sponsors") want to, they can create a single incentive for the entire process. E2E strategies do this. Since the rise of outsourcing in the 1980s, however, sponsors have a second option. If they want to they can create separate (and possibly different) incentives at multiple steps along the pipeline. This paper argues that the choice between E2E and PaYG is fundamental and that each strategy has generic strengths and weaknesses. Traditional distinctions between "push" and "pull" incentives fail to capture this distinction.[†] This section explores the generic strengths and weaknesses of End-to-End ("E2E") strategies. PaYG strategies are discussed in Section IV.

Before proceeding, we emphasize that the purpose of this paper is to determine which strategy are most likely to deliver a particular desired R&D effort at the lowest cost *to sponsors*.

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[*] Conceptually, the most convincing strategy would be for governments to announce a budget for new drugs and then destroy any un-spent currency at the end of every year. Paying high prices for existing drugs is almost as effective.

[†] Traditional distinctions differentiate between "push programs" that pay for R&D inputs in advance and "pull programs" that reward R&D outputs *ex post*. [1] However, "push" and "pull" make no distinction between incentives that encourage researchers to perform a specific task and incentive that postpone rewards until a finished drug is produced. Normally, a prize "for the most promising protein target discovered in 2005" and a prize "for the best new drug introduced in 2005" would both be considered "pull." The E2E/PaYG dichotomy emphasizes that these incentives are fundamentally different from one another.

A. *Generic Differences Between E2E and PaYG Strategies.*

By definition, PaYG schemes permit sponsors to implement different incentives at multiple points along the drug discovery pipeline. As we shall see, these can be either "push" or "pull" incentives. By contrast, E2E systems establish just one incentive for the entire process. In practice, no one argues that this incentive can be a "push" mechanism because that would mean paying researchers hundreds of millions of dollars in advance. [4] But this means that E2E sponsors can only use "pull" incentives. Compared to PaYG, E2E sponsors start with a smaller menu of options.

B. *Advantages of E2Es: Private Sector Decision Making.*

The principal benefit of E2E schemes is that they permit private sector researchers to manage the R&D process without sponsor interference. This strategy has undoubted political virtues, since it makes it easier for sponsors to disclaim responsibility if R&D fails. The benefits for economic efficiency are more obscure. Vesting control in the private sector only makes sense if non-profit entities are inherently less capable of "picking winners" than their corporate counterparts. We return to this question in Section IV.

C. *Problems With E2E: Setting the Reward.*

As previously noted, sponsors who adopt E2E strategies automatically limit themselves to "pull" incentives like prizes or APCs. These incentives share the generic weakness that sponsors must decide how large a reward to offer. If sponsors guess too low, no R&D occurs. If sponsors guess too high, they pay too much for any desired level of R&D. Sponsors could avoid both dangers if E2E systems were compatible with contract R&D[*], which lets sponsors set rewards based on sealed bids and other forms of competition that encourage researchers to reveal their true costs. Commercial pharmaceutical companies routinely use contract R&D to contain pre-clinical and human testing costs.

In general, the amount that E2E strategies overpay in expectation depends on how well sponsors can estimate the minimum reward needed to elicit R&D.[†] In practice, very little is known. Commentators who estimate the "minimum required market" for new drugs usually quote ranges in which the upper bound is 140% to 160% larger than the

[*] Like all incentive mechanisms, contract R&D has strengths as well as weaknesses. We argue below that the benefits outweigh drawbacks for pre-clinical and human trials. These programs reportedly account for three-quarters of all drug development costs. [5]

[†] In principle, sponsors can slowly raise the reward over time as long as growth does not substantially exceed normal corporate rates of return. [1] Unfortunately, this process takes a long time. Depending on how fast R&D costs rise, sponsors could wait ten to twenty years before R&D started. In some scenarios, R&D never starts at all. [6]

lower one. [6] On average, we expect sponsors to overpay by half this range or about twenty to thirty percent.*

It remains possible that sponsors can refine this estimate through more careful arguments. In what follows, we assume that a profit maximizing company will invest in R&D whenever the promised reward exceeds its per-drug development costs in expectation. We consider two cases.

What Reward is Needed to Elicit a Rich Nation R&D Effort? In the first case, we assume (somewhat unrealistically) that sponsors wish to replicate the R&D effort that is typically devoted to finding cures for rich nation diseases. The advantage of this approach is that it lets sponsors set rewards based on what commercial pharmaceutical companies actually spend. For example, DiMasi *et al.* use pharmaceutical company records to report that average per drug R&D costs lie between $684 and $936 million at the 95% confidence level. Here, the high estimate is 127% of the low estimate, suggesting that sponsors would only overpay by thirteen percent on average. [7] A second study, by Berndt *et al.*, is less favorable. It uses economic arguments to extract per-drug R&D costs from reported revenue data. [8] Although the study does not quote estimated errors, its methods appear generally consistent with the forty to sixty percent uncertainties described above.†

These estimates represent industry-wide averages. Since the amounts paid to develop individual drugs vary widely, it might be possible to obtain more accurate estimates for particular diseases. For now, it is unclear how sponsors would make such adjustments apart from guesswork. Similarly, R&D costs are known to vary from company to company. This suggests that some firms may be willing to perform R&D for a smaller reward. [9] The amount of this correction is also unknown.

What Reward is Needed to Elicit a Low Cost R&D Effort? The problem with per-drug R&D costs is that they say very little about what a minimum feasible ("bare bones") R&D program would cost. The reason is that companies in competitive industries set R&D investments equal to the expected value of whatever patents they hope to obtain. If Congress creates broad (*i.e.*, generous) patents, companies will engage in redundant and/or accelerated programs.‡ If Congress creates narrow patents, companies will mount

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*We assume that sponsors seek to elicit R&D activity with certainty and that probabilities are symmetrically distributed within the quoted range.

† Berndt *et al.* [8] argue that per-drug R&D costs should on average be equal to reported sales figures less marketing costs. Since marketing costs are unknown, their method effectively replaces uncertainty over one unknown (R&D expense) with another (marketing costs). They also make two *ad hoc* adjustments. First, they assert that published estimates of marketing costs – which vary from fifteen to thirty-six percent – are overstated and therefore adopt a ten percent figure instead. This yields a $2.56 billion estimate, which is approximately 140% larger than the figure that they would have arrived at using a 36% figure. They then increase their estimate to $3 billion (an additional 117% adjustment) on the ground that "a malaria vaccine may be more difficult to develop than the typical new chemical entity." *Id.* Since neither adjustment is based on detailed data, it is difficult to see how Berndt *et al.*'s estimate improves on the forty to sixty percent uncertainties quoted above.

‡ DiMasi *et al.* find evidence for this behavior in their data.

less ambitious programs. In either case, companies will end up earning the same (economic) profit in expectation – zero.

This analysis suggests that companies will respond to *any* reward that exceeds the minimum feasible amount needed to support a bare bones R&D program. However, it is still not clear how much money sponsors can save by offering smaller rewards. Kremer & Glennerster [1] argue that existing patent rewards are already near minimum feasible per-drug discovery costs. More specifically, they contend that Congress designed the Hatch-Waxman Act so that patent revenues would be constrained by the cost of developing follow-on, "me-too" drugs. One problem with this analysis is that it assumes that Congress knows what the minimum feasible cost of developing "me-too" drugs actually is. In fact, Congress seems to use the same DiMasi *et al.* estimates as everyone else. [6] In principle, a more direct method for estimating what a bare bones program would cost is to write down a *pro forma* budget. The Global Alliance for TB Drug Development has prepared a massive study along these lines. [5] It reports that a bare bones program could probably deliver new malaria drugs at between seventeen and twenty six percent of the range quoted by DiMasi *et al.* This figure remains controversial.[*]

Desired Level of R&D Effort. In keeping with our cost containment criteria, we have thus far assumed that sponsors would choose a bare bones program if that option were available. In fact, sponsors can choose any level from bare bones to rewards that exceed those found in rich nations. While the ideal level is a matter for public health authorities to decide, it is reasonable to think that they might want to spread their limited resources over as many programs as possible. Indeed, it is not obvious that high per-drug R&D costs are desirable even for rich nations. For example, multiple "crash" programs might be a poor investment if they only accelerated discovery by a few weeks or months. Similarly, large patent rewards might induce spending on non-R&D activities (*e.g.*, marketing, regulatory maneuvering, and lawsuits) that provide little or no benefit to patients.

D. *Problems With E2E: Controlling Sponsor Discretion.*

Researchers in E2E systems are not paid until after they have sunk their costs. This increases the incentive for sponsors to renege, since a researcher with sunk R&D costs can usually be persuaded to sell drugs at a price that barely covers its manufacturing costs. Knowing this dynamic, a rational company may refuse to invest at all unless it receives some combination of (a) legal and practical assurances that the sponsor will not renege, and (b) an additional premium to cover any remaining risk of default. From the sponsor's perspective, this creates an inherent tradeoff between the flexibility needed to

[*] Some commentators have criticized the MMV estimate on grounds that it assumes small clinical trial sizes, non-market cost data, and "highly conjectural" failure rates. [11] More generally, PPP budget estimates show "enormous variability" for reasons that are poorly understood. Commentators warn that they require "great caution." [12]

adjust rewards *ex post* to reflect true value of drugs and the size of the reward that must be offered *ex ante* to elicit R&D in the first place.

In practice, one can imagine many possible tradeoffs between flexibility and reward size. For example, a blue ribbon panel recently argued that sponsors should not be allowed to adjust APC rewards downward even if R&D costs fall in the interim. [10] Presumably, they believed that the increased discretion was not worth the additional risk premium that companies would demand in compensation. Other possible tradeoffs include promising to award a fixed sum to the best drug(s) produced within a pre-announced time frame [3, 4] or promising to calculate prizes according to a pre-announced algorithm [3]. Although both methods still run the risk of under- and over-rewarding innovation, these errors may be smaller than those associated with a fixed, *ex ante* reward.

E. *Problems With E2Es: Cumulative Innovation.*

The final generic difficulty that E2E systems face involves second-generation inventions. In conventional patent systems, improved products command a higher price and earn more revenues. In order to share in these revenues, first-generation patent owners must grant licenses that permit improved products to appear on the market.

The result is very different for E2E systems. Consider first a simple APC strategy in which sponsors announce a single fixed price in advance. Since prices are fixed, an improved product cannot earn more revenue than the first generation product does. For this reason, the first generation inventor has no incentive to improve its own product or make its technology available to others. Instead, its best strategy is to block the better product until, in Farlow's phrase, the sponsor agrees to pay an additional, "monopoly-size bonus." [9] In principle, sponsors can fix the problem by announcing a second, higher reward for second-generation products. However, the amount of this reward will normally be even more speculative than it is for first-generation products. A better solution might be for sponsors to insist that first generation inventors license all improvements at zero royalty. However, this solution is also sub-optimal since researchers may not perform first-generation R&D in the first place if they cannot share in second-generation revenues. [4]

Hollis' QALY-based prize system tries to evade these problems by using an algorithm to calculate the incremental value added by each new drug. [3] Since only the algorithm is fixed, data (and reward) can be updated continually. The weakness of this system is that QALY-based estimates of social value are not particularly accurate or replicable. [6] If these drawbacks are severe, sponsors will do better to estimate the reward in advance.

IV. Pay-as-You-Go Strategies

Unlike E2E systems, PaYG systems place substantial decision-making and outsourcing responsibilities in the hands of non-profit managers. We begin by asking what strategies PaYG managers are likely to follow. We then turn to potential problems that might make PaYG less efficient than comparably funded E2E strategies.

A. *Tailoring Incentives For Specific Problems.*

Commercial pharmaceutical companies currently use multiple incentives to outsource R&D, including (a) purchasing contract research services, (b) purchasing patented knowledge from outside entities, and (c) awarding prizes to researchers that solve particularly difficult problems.[*] PaYG sponsors must design strategies that replicate and, if possible, improve on these incentives. Here, we comment on the choices that PaYG sponsors are likely to make at different points along the drug discovery pipeline.

Basic Research. Basic science requires intense individual creativity and hence researcher discretion. Furthermore, researchers frequently need to assemble widely-scattered information. Grants facilitate these goals by rewarding applicants who submit new ideas. Since researchers who fail have less chance of winning future awards, grants also provide limited assurance that recipients will not exploit their discretion to shirk work. Finally, grants pay for R&D in advance. This is an important advantage for academic scientists and other groups that lack access to financing.[†] [4]

Early Phase Drug Discovery. Early phase drug discovery encompasses multiple steps ranging from developing new drug ideas to optimizing small molecules that can be tested as drug candidates. Once again, researchers must draw on widely scattered knowledge and exercise substantial discretion. One natural solution would be for sponsors to extend the grant model beyond basic research. For now, commentators disagree about whether academic scientists are sufficiently interested in applied research for grants to be effective. [1, 13] The only way to be sure is to try the experiment.

The main alternative to grants is for sponsors to award "best entry prizes" to whichever researcher(s) achieve the most important results in a pre-defined period. Like patents, prizes are a powerful method for eliciting new ideas. Since researchers cannot claim a prize without concrete results, best entry prizes also provide substantial protection against lazy or inefficient researchers. Best entry prizes are already widely used to solve chemical engineering problems. [6]

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[*] Companies competing in an E2E system would presumably use these same strategies. The main difference between E2E and PaYG strategies lies in who pockets the savings.

[†] Lack of financing is the main reason why prizes are disfavored. Historically, academic prizes have elicited many new discoveries. [4]

Finally, PaYG sponsors might experiment with "open source drug discovery" collaborations in which members search for protein targets and compounds in much the same way that programmers find and fix bugs in LINUX. The rise of computational biology – which requires few physical resources beyond volunteers and computer terminals – provides the closest analogy to open source computing. [14] As in LINUX, the fact that members are volunteers means that they have little incentive to shirk work.* More speculatively, some authors argue that open source methods can also be used to perform experimental chemistry. Chemistry, however, requires reagents and other expensive inputs. Volunteers would have to divert these resources from existing grants. [14, 15] How long funding agencies would tolerate such a situation is anyone's guess.

Pre-Clinical and Clinical Testing. The number of potential drug compounds is so large that there is almost no chance that a new drug candidate has been studied before. Because scientists must experiment *de novo*, the ability to elicit information is much less important than for earlier R&D phases. On the other hand, pre-clinical and human testing are extremely expensive. This suggests that incentives should focus on cost containment. One natural solution is to award R&D contracts to whichever researcher offers the lowest rate, either informally or through competitive bids. The main drawback of this method is that contract researchers may have an incentive to shirk or else prolong unnecessary work after the contract is signed. Fortunately, preclinical and human testing are extremely routinized and generate massive paper trails. These facts facilitate monitoring and suggest that any moral hazards are manageable. Large pharmaceutical companies routinely purchase preclinical and clinical testing services from contract researchers.

A second, more speculative option would be to organize open source clinical trials. Eric von Hippel [16] has suggested that clinicians might organize open source trials aimed at finding new, "off label" uses for previously approved drugs. Off label trials are particularly suitable for open source because the healthcare system usually pays the underlying cost of drugs and physicians. Extending open source models to earlier, pre-approval testing would mean finding other sources of funding. In principle, pharmaceutical companies might be willing to fill this gap if FDA regulators concluded that open source data were inherently convincing. Under the current system, contract researchers sometimes color or even falsify results to please their employers. [6]

Manufacturing. Competition is a powerful constraint on manufacturing costs. Historically, sponsors have used contracts to purchase a fixed quantity of drugs as an incentive to build new manufacturing capacity. Examples include polio and, more recently, bird flu vaccine. [6] Competition is also a powerful way to constrain manufacturing costs once production begins. By far the simplest strategy is for PaYG sponsors to put drug compounds in the public domain so that anyone can manufacture them.†

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* The corresponding drawback of using volunteers is that the supply is more or less fixed. Paying researchers to volunteer turns open source into a grant model.

† This solution breaks down where the market is too small to support more than one or two entrants. In this case, sponsors should award competitively bid contracts to whichever manufacturer offers to sell drugs at the lowest price.

B. *Problems with PaYG Schemes: Inadequate Purchasing Power.*

So far, we have assumed that non-profit PPPs can outsource R&D just as efficiently as large pharmaceutical companies. However, we have already noted that contract researchers may have an incentive to shirk and/or needlessly prolong work. Commercial pharmaceutical firms use large liaison staffs and the prospect of repeat business to discourage such practices. [17] These facts suggest that large entities may have an inherent advantage at extracting value from outsourced research. This could be a significant handicap for individual PPPs, whose annual budgets are seldom more than a few percent of what large pharmaceutical companies spend on R&D.* [6]

It is possible to put an upper bound on the size of this handicap. Press accounts report that R&D service providers typically earn ten to fifteen percent profit margins.† [17] Assuming a ten percent return to capital, this suggests that companies providing R&D services earn super-normal profits of no more than five percent. Large pharmaceutical companies should not be able to extract discounts greater than this figure.

C. *Problems with PaYG Schemes: Picking Winners.*

Advocates of E2E systems often argue that non-profit firms are less able to pick and develop winning drug candidates than their private sector counterparts. Since many PPPs hire executives directly from private industry, this cannot be a matter of individual competence. If the effect exists at all, it must be a matter of incentives.

In the private sector, efficiency ultimately depends on the abililty and willingness of profit-maximizing shareholders to de-fund companies that fail to perform. In the non-profit world, sponsors play this role. Unfortunately, current PPPs often combine drug management, education, advocacy, and other functions within a single entity. This bundling makes it hard for sponsors to de-fund entities that do just one of these tasks (*e.g.* drug discovery) badly. In principle, reform should be straightforward.

The deeper question is whether sponsors are willing to de-fund failures as ruthlessly as a private shareholder would. Presumably, they should ask themselves this question before adopting a PaYG strategy. In the meantime, critics of public sector R&D sometimes point to instances in which researchers have failed to deliver vaccines in the past. [1] Less often noticed are the many instances in which government and non-profit entities have succeeded. Examples include the US Army (Argentine hemorrhagic fever, Venezuelan equine encephalitis, Rift Valley fever, tularemia, infant botulism) [18], The

* In principle, PPPs can ameliorate the effect by improved monitoring and bargaining practices, pooling purchases, and finding small vendors who are more likely to value their business. Sponsors can also make PPP buying power more credible by providing long-term funding.

† Quoted margins are for the chemical industry. Margins for industries might be different, although most R&D services seem to be competitively supplied. [6]

March of Dimes (Salk and Sabin polio vaccines) [19] and The Pasteur Institute (rabies, BCG vaccine, yellow fever, polio, hepatitis B, shigellosis). [20] Pending detailed investigation, there is no particular reason to think that non-profit entities are inherently inefficient.*

VI. Mixed Strategies.

So far, we have assumed that PaYG and E2E strategies are distinct from each other and also from conventional patent incentives. Here, we ask how these distinctions can be relaxed to create "mixed" incentives.

A. *Extending E2E or PaYG Rewards to Include Patent Revenues.*

Patents are an unnecessary complication for diseases like leishomaniasis or Chagas, where commercial markets are negligible. However, there are many diseases where patent revenues provide a substantial (albeit still inadequate) fraction of the reward needed to elicit R&D. Some observers claim that patent revenues for new tuberculosis drugs could generate up to eighty percent of the reward needed to elicit innovation. [1] Smaller, but still significant markets have similarly been estimated for tuberculosis (45%) and AIDS (25%). [5, 21] While these estimates are probably optimistic, it is worth asking how patents can be grafted onto E2E and PaYG strategies.

Adding Patents to E2E. E2E strategies leave R&D decisions in the hands of industry. The most natural way to extend these strategies is to let the industrial partner own patent rights over and above the basic E2E reward. Alternatively, sponsors can dispense with E2E rewards entirely by paying a subsidy to the private partner's R&D program. In either case, sponsors face the usual difficulty of deciding how much reward is actually needed to elicit investment. Now, however, this problem is harder because the private partner can usually estimate the value of patent rights better than the sponsor can. This increases the sponsor's risk of overpayment.

Adding Patents to PaYG. PaYG systems leave R&D spending decisions in the hands of sponsors. The most natural way to extend these strategies is for a commercial pharmaceutical company to contribute money and services to the sponsor's R&D program in exchange for the right to patent whatever drugs are ultimately produced. Currently, sponsors and their PPPs usually negotiate such transactions with one pharmaceutical company at a time. The problem with this approach is that the sponsor's ability to extract money and services is limited by its ability to estimate how much revenue a patented drug is likely to earn. A better system would be for the sponsor to

* One variant of the "picking winners" argument is that PaYG sponsors might produce drugs that society has no use for. By contrast, E2E systems are tied to market signals. The problem with this analysis is that E2E markets are massively subsidized. This means that market signals are fairly weak. Furthermore, infectious diseases have large externalities. This suggests that public health authorities – and PaYG solutions – may be able to judge the social value of drugs better than markets can.

auction its patent rights to whichever company offers the most money and services. This competitive system would encourage companies to reveal their true estimates of potential patent revenue.

When Can Sponsors Use Patent Rights to Stretch Their R&D Budgets? Patents have drawbacks as well as benefits. If drugs are patented, high prices will almost always exclude some users. From the sponsor's standpoint, this means that patent-supported research delivers fewer benefits than a publicly-funded program that puts new drugs in the public domain. From a cost-benefit perspective, this may sometimes be an acceptable tradeoff – as, for example, when a publicly-funded program would be unaffordable.

Sponsors frequently try to expand patient use of patented drugs by insisting that commercial pharmaceutical companies offer deep discounts ("access pricing") to poor patients. However, access pricing automatically reduces profits and, indirectly, the amount of money and services that pharmaceutical companies are willing to contribute to R&D in the first place. The question is, how much? The answer will normally depend on the private partner's ability to price discriminate by charging different prices to different users.

Suppose first that price discrimination is impossible so that the pharmaceutical company must charge a single price to all patients. In this case, company's expected patent revenues will disappear – along with its willingness to contribute resources – once the access price falls below marginal cost of production. Judging from the fact that several vaccines sold at marginal cost still only reach a small fraction of users [1], it may often be necessary to set access prices at or below the marginal cost of production. In this case, patents provide no net benefit to sponsors although they may shift expenses in time and/or from one sponsor to another.

Now suppose price discrimination is perfect. In this case, manufacturers can offer deep discounts to the poorest patients with no effect on patent revenues. In fact, profit-maximizing manufacturers will *automatically* offer such discounts until prices reach their marginal cost of production. This means that sponsors should only subsidize production if the desired access price is below marginal cost.

The foregoing discussion suggests that sponsors should measure potential patent revenues not only by the "revenue maximizing price" that the private partner could theoretically charge, but also by the access price. In general, patent revenues will be most useful where price discrimination is strong. The most favorable cases almost certainly involve diseases where the "commercial" market is geographically separate from the LDCs whose citizens need access pricing. In these cases, the simplest solution (following Lanjouw [22]) may be to limit company patent rights to rich nations.

B. *Mixing E2E and PaYG.*

Advocates commonly argue that sponsors should fund a mix of E2E and PaYG systems. Political motivations aside, the justifications for these proposals are obscure. In principle, there are at least two reasons why a mixed strategy might make sense. First, sponsors may not be able to decide whether E2E or PaYG is the most cost-effective proposal and might want to experience both systems before choosing. However, the time scale for developing drugs is twelve to fifteen years. Even if sponsors are able to form a decision in some fraction of this time, such an experiment is likely to be expensive.

Second, sponsors might want to combine E2E and PaYG if commercial firms and public entities each had areas of comparative advantage. For example, commercial firms might be better at "picking winners" while PPPs might have superior knowledge about which drugs are needed. In this case, sponsors might want a strategy in which PPPs subsidized pharmaceutical companies that pursued particularly useful drugs. Unfortunately, it is not obvious how this scenario would be implemented in practice. To the author's knowledge, no advocate of mixed solutions has ever suggested criteria that sponsors could use to apportion funds between E2E and PaYG initiatives.

Finally, there is an important reason why sponsors might *not* want to fund E2E and PaYG strategies simultaneously. As we have noted, the best way for E2E systems to overcome researcher mistrust is through large, frequent payouts. Conversely, we have argued that PaYG methods are more efficient when PPPs can offer large volumes of repeat business. This observation suggests that both strategies feature substantial economies of scale. Mixed strategies dilute this advantage by dividing funds between competing schemes.

VII. Conclusion

Conventional patent incentives have failed to cure diseases of poverty.[*] This paper has evaluated alternative strategies based on their ability to control costs. Although E2E proposals seem to emulate the patent system, PaYG strategies may be less expensive for sponsors. Based on existing evidence, an E2E strategy could well cost twenty to thirty percent more than comparable PaYG efforts. For now, the best argument for accepting this penalty is that E2E systems leave R&D decisions in private hands. However, this only matters if private sector drug management teams can "pick winners" more efficiently than their non-profit counterparts. While many people believe this assertion, the evidence is unclear. Ultimately, the most important factor may be whether sponsors are willing to de-fund inefficient drug management teams as ruthlessly as a private sector shareholder would.

Advocates of E2E solutions sometimes suggest that their solutions are closer to the patent system – and therefore more conservative – than PaYG alternatives. In fact, it is more accurate to say that *every* solution is radical. And yet we must choose. Modern

[*]The problem is not confined to diseases of poverty. Patents have also failed to deliver new vaccines for biological weapons. Congress is currently funding several programs to fix the problem, including a $5.6 billion E2E initiative called "Bioshield." To date, none of these programs has been notably successful.

innovation economics teaches that there is no single "best" institution for every innovation problem. [4] Given that every R&D institution is flawed, the best we can do is make hard choices about which flaws we are willing to live with. No amount of discussion will produce an "ideal" solution and it is both pointless and irresponsible to wait for one.

We should not overstate the challenge. The worldwide R&D budget for diseases of poverty is fairly small by corporate standards. Each year, Bill Gates decides which Microsoft R&D programs are likely to yield the most benefits and allocates the company's $7 billion R&D budget accordingly. For him, R&D is just another business judgment to be decided on coolly dispassionate dollars-and-cents criteria. The Gates Foundation could do worse than follow his example.

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