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Abstract:

We propose a 2-stage procurement model of public-private partnership to provide better incentives for R&D on neglected diseases. The model combines advance market commitment, subsidized clinical trials, and rewards based on therapeutical contributions of new drugs through a prize screening mechanism. The model is primarily intended to facilitate small firms' R&D by providing cash flow, rewarding quality of new drugs, and sharing risks and costs of new drugs development, while limiting moral hazards. The model's advantages include reduction of overpayments, better disclosure of information, provision of production licences, and direct targeting of better quality drugs.

Key words: neglected diseases, prize screening, pharmaceutical R&D

JEL classification: I12, I18, D82, H41

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1. Introduction

Most diseases have a patient base lacking in numbers and/or purchasing power for blockbuster sales, in turn attracting large-scale commercial R&D (Bartfai and Lees, 2006: 14, 71). This is especially true for orphan diseases with low patient bases in rich countries and neglected diseases (NDs) with low purchasing power in developing countries. In both cases, some public intervention is needed to bring about the creation of new drugs.

The need to design incentives aimed at developing R&D in these two groups of diseases is the source of an intense debate in the literature and has generated several public interventions such as the initiative of the Center for Global Development (CGD) (2005) and public-private partnerships (PPPs). CGD proposes the Advanced Purchase (or Market) Commitment (APC) plan for vaccines with heavily subsidized co-payments for large quantities of new vaccines with pre-specified characteristics. PPPs are non-for-profit project-based organizations which reduce the risks and costs of R&D by involving governments, private subcontractors like pharmaceutical firms or clinical research organizations (CRO) and philanthropic organizations.

There has been criticism of both the APC (Farlow, 2004; Light, 2005) and PPPs (Sarewitz, Foladori et al., 2004: 72-83). But overall PPPs are seen as a better option being organizationally flexible and more cost efficient. The majority of recent new drugs for NDs have been developed through PPPs, which provide a risk sharing mechanism for innovators (Moran, Ropars et al., 2005).

One objection to the APC raised by both Light (2005) and Farlow (2004) is that only large pharmaceutical corporations may have enough cash to finance R&D. This

matters given the role of small firms in developing new drugs. Villa, Compagni et al. (2009) demonstrated that the majority of new drugs approved under Orphan drug laws targeting diseases with small patient bases have been developed and produced by small and medium sized pharmaceutical firms. 35% of all R&D projects on diseases relevant to Africa between 1980 and 2004 and the majority of orphan diseases drugs have been developed by start-up biotech companies (Pammolli and Riccaboni, 2007:154). Almost half of all research projects for NDs under PPPs were conducted by small companies (Moran, Ropars, et al., 2005).

This paper develops a model primarily intended to facilitate R&D of small firms by providing cash flow and sharing risks and costs of new drugs development, while limiting moral hazards.

Section 2 describes the model which combines advance market commitment, subsidized clinical trials, and rewards based on therapeutical contributions of new drugs through a prize screening mechanism. Section 3 formalizes the model following the contract theory literature. Section 4 presents the estimations of the expected costs of our scheme and it is followed by the conclusion

2. Description of the proposal

Our proposal combines three ideas. The first idea is the proposal of Kremer and Glennerster (2004: 104) of bonus payments to drug innovators based on disability-adjusted life-year (DALY) criteria. Hollis (2006: 130) and Pogge (2006: 146-147) propose rewarding new drugs in proportion of their realized therapeutic effects. The

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second idea is public funding of clinical trials and health value-added pricing (Jayadev and Stiglitz, 2009; McGuire, Drummond et al, 2004). The third idea is virtual pharmaceutical companies based on outsourcing, which has been a realized business model in the industry. According to PAREXEL (2004: 36), the top ten pharmaceutical companies as measured by the number of products in development as of March 2004 had 42.8% of all their drugs in R&D licenced-in. PWC (2009:6) predicts the appearance of a new dominant model of pharmaceutical R&D, which consists of a network of organisations with a common purpose and a network based company, which will outsource most of its activities while managing a research portfolio.

The aim of the proposed 2-stage public-private partnership Program (2-SPPP) is to (i) reward selected innovators for their drug candidates submitted to the Program with a fixed prize, (ii) then outsource and pay for clinical trials and evaluation of therapeutic quality of the drug candidates to independent professional organizations through competitive bids, (iii) assist and pay for drug approvals for successful drug candidates, and finally (iv) provide a second prize to innovators based on a formula for the evaluated quality of a successful drug in phase III of clinical trials.

The implementation of our proposal requires the following steps:

1. In order to launch and supervise the 2-SPPP a board of directors is formed from representatives of sponsors and recipient developing countries affected by NDs. A reputable international development organization with a UN mandate such as the World Bank can provide special preferential loans to developing countries to finance this Program. The reputation of the World Bank could have the advantage of reassuring inventors that the Program financial commitments will be fulfilled.

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2. The board of directors select through a competitive tender an operating non-profit virtual pharmaceutical company (NVC) with experience in management of pharmaceutical R&D and work in developing countries. The NVC must publish clear criteria for the selection of a drug candidate into the Program, publicly explain their drug selection and financing decisions, promptly publish clinical trials' results, monitor subcontracts based on competitive bids, and channel two payoffs to the winning firms.

3. The NVC must periodically call for submission of drug candidates from all innovators having demonstrated a proof-of-concept or received investigational new drug (IND) status from recognized pharmaceutical regulation authorities. Such submission should include a drug candidate's results of preclinical pharmacology and toxicology tests; an estimation of expected costs of industrial production of the proposed drug for a specified scale; a specification for administration, stability, and storage conditions of a the drug; a commitment to issue a licence to conduct trials and put the production and distribution licence in the developing countries of the drug in public domain; an outline of the clinical development strategy; a consent that all results of clinical trials will be promptly published.

4. The NVC must choose an independent evaluator to conduct cost-efficiency analysis of new successful drugs based on phase III clinical trials if a drug candidate reaches this phase. McGuire (2001) concludes that cost-efficiency analysis is a consistent tool in comparing alternative health products and it might work as a proxy for welfare maximization, especially when patients do not bear full costs of their health care or markets do not exist. Drummond (2007) notes that ten countries introduced some cost-

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benefit or cost-efficiency analysis for national drug reimbursement policies and he concludes that such a decision process is workable.

The evaluator must come to a consensus methodology for cost-benefit analysis to be approved and published by the board of directors. Based on the results of the clinical trials, the evaluator will give an estimation for the expected ratio of QALYs (DALYs) saved by a new drug per $1 of expected drug manufacturing costs, which is referred further as *drug quality*. For each disease, a benchmark drug or treatment and its quality must be estimated and announced before the selection of drug candidates into the Program.

5. The NVC recruits part-time pharmaceutical consultants to evaluate/review drug candidates and to advise on clinical trials and the drug approval process. All bids, submissions, transactions, and decisions of the NVC are promptly published on the Program website to encourage public monitoring and health forums facilitated by the Program.

6. The NVC together with the consultants select a pre-specified number of *n* drug candidates. The selection should be based on a predetermined weighted average "promise index" of the expected candidate's manufacturing cost, performance indicators in the pre-clinical phase, projected storage conditions, and ease of administration. The promise index is worked out by consensus among the consultants. The drug candidates with the highest promise index are selected for further fully subsidized proof-of-concept (POC) studies. Selected on POC results by the NVC, drug candidates progress into clinical trials in developing countries sponsored by the donors. Paul, et al (2010: 206-207) suggest that

the cost of such studies can range from \$6 to \$22 million and they emphasize the crucial role of drug portfolio selection and POC studies to increase research productivity.

7. Selected inventors are paid a fixed amount, the first pre-announced fixed prize (F), in exchange for a licence for clinical trials, production, and distribution of the drug in developing countries. This prize intends to stimulate pre-clinical research by liquidity constrained inventors. However, the amount of the first stage prize F is set at a lebel below the expected costs of the drug candidate discovery to discourage entrance of applicants with low quality candidates.

8. The NVC contracts out clinical research organizations (CRO) through competitive bids to conduct trials with the selected candidates. The establishment in 2003 of the European and Developing Countries Clinical Trials Partnership for building capacity for the clinical trial (Kaplan and Laing 2004:102) is already a step in that direction. The number of candidates n is determined in the light of budget constraints and expected attrition rates. CROs must submit monthly reports of clinical trials to be posted on the program's web site. The NVC has the right to stop and alter clinical trials of a drug candidate in case of a drug's non-performance or safety concerns. A new drug candidate is tested against a pre-announced typical drug or a therapy. Sculpher, Claxton et al. (2006) conclude that randomised controlled trials are the key for cost-effectiveness analysis and that patient population, period, research design and proper comparators must be specified for such analysis.

9. A successful drug candidate after clinical trials is further facilitated with registration and then is awarded the second prize (S) in an amount proportional to its estimated drug quality as defined by the pre-specified formula. To reduce moral hazard

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on the side of inventors, drugs of a quality lower than the benchmark drug for a disease are not eligible for the second prize. The NVC is paid bonuses per number of processed drug candidates to enhance management incentives to drop non-performing candidates.

3. Model formalization

The formalization of the model follows the contract theory literature (Salanie, 2005) with a prize screening through rewards. The Principal, e.g. the board of the Program directors together with the NVC, maximizes the number of quality drugs given the budget by setting three major controls: the amount of the first prize F, the second prize S and the number of drug candidates n. The Principal sets the prizes to discriminate against low quality drugs by fixing incentive compatibility constraints for innovators while encouraging their participation in the Program. The drug innovator (the agent) maximizes discounted net payoff from the two prizes.

Drug quality is not perfectly observable and is uncertain even for innovators so that a non-price mechanism such as experts' opinions is needed to admit a candidate into clinical trials. However, the proposed incentives should encourage the submission of only the most promising drugs, which is also conducive to the reduction of the costs of clinical trials. There is a trade-off between setting the first prize high enough to provide cash flow for innovators and reducing incentives for submission of low quality candidates. The latter must be a priority for the sake of the social surplus.

The model assumes a fixed number of T years required for a drug development, but R&D costs (R) at the preclinical stage and costs of clinical trials (C) may depend on

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drug quality θ. Suppose benevolent sponsors have a current budget B to maximize QALYs saved from a particular disease. Sponsors can purchase B/p treatments of a drug priced at p per treatment. If one treatment saves D QALYs, sponsors can save $D/pB = \theta_0 B$ QALYs, where $\theta_0 = D/p$ is the quality of the benchmarking drug defined as number of QALYs saved per unit price of the drug. Let sponsors invest $C+R$ into R&D of a new drug of quality $\theta > \theta_0$ with probability of success q in T years, where C is the cost of clinical trials plus registration. This is a reasonable decision for risk neutral sponsors if discounted with some rate d the number of QALYs saved from the purchase and distribution of the new drug and some purchase in the amount of A of the current drug are greater than QALYs saved from purchase of the current drug:

$$\theta_0 B \geq A\theta_0 + q(B\text{-}A\text{-}C\text{-}R)\theta e^{(r\text{-}d)T} \rightarrow \theta > \theta_0(B\text{-}A)e^{(d\text{-}r)T}/(q(B\text{-}A\text{-}C\text{-}R)) \qquad (1)$$

where r is the discount rate of capital for sponsors, which increases the available budget of the sponsors to purchase the new drug in T-th year at e^{rT}. The amount of A spent on purchasing of the current medicine is determined by sponsors' utility of QALYs.

Inequality (1) shows that developing a new drug make sense for sponsors if its quality is significantly higher than the quality of the existing drug as right hand side multipliers are all greater than one: $(B\text{-}A)/(B\text{-}A\text{-}C\text{-}R)>1$, $1/q>1$, and $d>r$ assuming that sponsors' discount rate for QALYs is greater than discount rate for their capital. Inequality (1) can be used to set a threshold (benchmark) drug quality for a public drug R&D Program: $\theta \geq l\theta_0$, where $l = (B\text{-}A)e^{(d\text{-}r)T}/(q(B\text{-}A\text{-}C\text{-}R))$. A rough estimation of this threshold is about $l=5$ assuming 3% discount rate on DALYs used by WHO (2008) in estimation of the global burden of diseases, 1% discount rate for the World Bank's

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development loans, $T=10$ years, $C+R<<B-A$, and, according to DiMasi et al (2004), the average probability of success in clinical trials is $q=0.23$. This means sponsors might find it irrational to invest in its R&D unless a new drug's quality θ is less than 5 times better than that of the existing drug quality θ_0.

Consider a simplified problem of risk neutral donors maximizing the QALYs saved from a possible new drug development and a current drug for the total drug purchase in amount of A in the proposed 2-stage Program:

$$\max_{F, S(\theta)} \quad (\theta Ame^{(r-d)T} - F - S(\theta) - C(\theta) - A)q + (1-q)(\theta_0 Ame^{(r-d)T} - F - S(\theta) - C(\theta) - A)$$

subject to

firms' participation constraint: $\quad F + S(\theta) - R(\theta) \geq V > 0$

incentive compatibility constraint 1: $F + S(\theta_0) - R(\theta_0) \leq 0$

incentive compatibility constraint 2: $F + S(\theta) - R(\theta) \geq F + S(\theta_0) - R(\theta_0)$, $\theta \geq \theta_0$

where F, $S(\theta)$ – the first and the second prizes, V – expected profit of the representative firm outside of the Program, i.e. from commercial drug development; m – social value of one QALY. The participation constraint states that the representative firm must obtain at least the same profit from participation in the Program than from an outside option. The first incentive compatibility constraint states that the firm's payoff from a low quality drug, which is here assumed at the level of the benchmarking drug θ_0, must not be a positive one to prevent entry of firms with what they already know to be a low drug quality candidate $\theta \leq \theta_0$. The second constraint requires that the payoff for a better quality drug must be greater than the payoff for a drug candidate comparable to the benchmark level.

Assuming interior solutions ($F>0$, $S>0$), Kuhn-Tucker conditions to this problem are:

$\lambda 1 - \lambda 2 - 1 = 0,$

$\lambda 1 \geq 0, \lambda 2 \geq 0, \lambda 3 \geq 0,$

$F + S(\theta) - R(\theta) - V \geq 0, \lambda 1(F + S(\theta) - R(\theta) - V) = 0$

$R(\theta_0) - F - S(\theta_0) \geq 0, \lambda 2(R(\theta_0) - F - S(\theta_0)) = 0$

$S(\theta) - S(\theta_0) + R(\theta_0) - R(\theta) \geq 0, \lambda 3(S(\theta) - S(\theta_0) + R(\theta_0) - R(\theta)) = 0$

$qAme^{(r-d)T} + (\lambda 1 + \lambda 3 - 1) S'(\theta) - R'(\theta)(\lambda 1 + \lambda 3) - C'(\theta) = 0$

where $\lambda 1$, $\lambda 2$, and $\lambda 3$ are Lagrange multipliers for the participation, the incentive compatibility 1, and the incentive compatibility 2 constraints respectively.

The constraint 2 is not binding as its right hand side is not positive, whereas its left hand side is positive according to the participation constraint; hence $\lambda 3 = 0$. The participation constraint must be binding: otherwise it would be possible to increase the first and the second payment by an infinitesimal amount without violation of the constraint. Such an increase in the payments would diminish the objective function; hence, the objective function is not maximized when the constraint is not binding. Similarly one must conclude that the incentive compatibility constraint 1 must be binding: $F + S(\theta) - R(\theta) = V$ and the incentive compatibility constraint is $F + S(\theta_0) - R(\theta_0) = 0 \rightarrow F = R(\theta_0) - S(\theta_0)$. Normalizing the second payment for drug quality $\theta \leq \theta_0$ at zero to discourage entry of low quality candidates: $S(\theta_0) = 0 \rightarrow F = R(\theta_0)$. Hence, the Kuhn-Tucker conditions are simplified with $\lambda 3 = 0, \lambda 1 > 0, \lambda 2 > 0$ to

$Ame^{(r-d)T} = R'(\theta) + C'(\theta)$

Simplifying to $C'(\theta) = 0$, i.e. assuming that the costs of clinical trials are independent of drug quality, and taking into account differentiation of the participation condition

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$S'(\theta)= R'(\theta)$, then $S'(\theta)= Ave^{(r-d)T}=k$ – a parameter. The solution to this equation is

$S = k\theta +k_0$. Given that $S(\theta_0)=0= k\theta_0 +k_0 \rightarrow k_0 = - k\theta_0 \rightarrow S=k(\theta – \theta_0)$, i.e. the second

optimal payoff must be set in proportion to the marginal drug quality $(\theta – \theta_0)$. In this case

marginal incentives for drug quality are constant and equal k and independent of

probability of success q. We hypothesize that this linear incentive provided by the second

prize can still be robust even in the case of risk-averse firms (see the discussion of

advantages of linear contracts by Holmstrom and Milgrom (1987)).

Consider now the risk-neutral innovator problem of maximization of the net

payoffs from the Program by quality θ:

$$\max_{\theta} \quad q(Fe^{-rt(\theta)} + k(\theta – \theta_0)e^{-rT} – R(\theta)) + (1-q)(Fe^{-rt(\theta)} – R(\theta))$$

where $t(\theta)$ is time of pre-clinical R&D. The first order condition is

$qke^{-rT} = Frt'(\theta)e^{-rt(\theta)} +R'(\theta)$

assuming $t'(\theta)>0$ as time of research and pre-clinical R&D costs $R'(\theta)>0$ are

proportionate to drug quality and $R'(\theta) = b$ is a small number in comparison to

$Frt'(\theta)e^{-rt(\theta)}$, the first order condition can be expressed as

$t'(\theta)=qke^{-r(T-t(\theta))}/(Fr)$ this implies that under the Program the firm chooses drug quality θ

and related R&D time in proportion to $qke^{-r(T)}/(Fr)$. Therefore, the managing company

can increase k to enable targeting of higher drug quality by the firm as payoff increases in

θ. The coefficient k must be set in consultations with the industry and sponsors. The NVC

can also increase the probability of success q by exercising care in the choice of a

portfolio of drug candidates. Assuming that the social value m of one QALY is

approximately the annual national income per capita in low income countries, which is

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around $1000, then the parameter k can be set as $k=Ave^{(r-d)T} \sim 1220A$ assuming r=3%, d=1%, T=10 years.

4. Calibration of the model

The outside option for a small firm can be approximated by participation in the orphan drug development scheme, which might provide the net present value of a stream of profits from annual $500 million sales of an orphan drug for 15 years of effective patent life and exclusive marketing rights applying an annual discount rate of 15%. Our discount rate of 15% follows from the estimations of Taylor (1999: 144) for the internal rates of return that ranged from 11.37 to 22.46% for a dozen of top American pharmaceutical companies between 1975 and 1991. Vogel (2007: 74) noticed that top pharmaceutical companies enjoy 23.6% net profit before taxes so that we assume that 20% of those a half of billion sales are translated into net profit, which is $V \approx$ $585 million in net present value.

Kaplan and Laing (2004: 101) summarized five sources of estimations and concluded that direct preclinical development costs ranged from $8.33 to $26.0 million. Preclinical tests of drug candidates for tropical infectious diseases can serve as a good proxy for success in clinical trials while preclinical trials costs are estimated at $20 million (Hopkins, Witty et al. 2007).

Let us consider the major ND – tuberculosis. According to the report of the Global Alliance for TB Drug Development (2001: 40,47,52-57) the out-of-pocket costs of the preclinical phase for a new anti-tuberculosis (TB) drug is about $5 million and

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preclinical safety studies can be accomplished in 82 weeks. The out-of-pocket costs of all clinical trials for a new anti-TB agent in developing countries such as India and South Africa would be about $9.9 million and would last 7-10 years. In a developed country, costs of phase I anti-TB drug trials were about $0.65 million, phase II – $3.4 million, phase III – $22.6 million, but for Uganda, similar costs are much lower: phase I - $0.16 million, phase II – $1.6 million, phase III – $8.2 million. Based on this data, in the case of tuberculosis in year 2000 prices, the first payment can be set at F=$5 m, the second payment to be set at about S~V-F =$585 m - $5 m = $580 m for a good drug, though the second payment is set in proportion to the desired drug quality by adjusting the parameter *k*.

Estimated probabilities for an anti-infective drug candidate is 0.661 for entering the phase II of trials and 0.382 for phase III (DiMasi et al, 2004). This implies out-of-pocket expected costs of a TB drug candidate clinical trials in Uganda at $0.16 m + 0.661*$1.6m + 0.382*$8.2 m ~ $4.5 m. Thus, expected Program costs would be ($4.5 m +$585 + $10 m) *1.2 = $719.4 m. The coefficient 1.2 includes 20% overhead costs, which are estimated at 20-30% for a commercial research projects (Paul, et al, 2010) to run the Program administration.

A firm might find it quite attractive to invest in pre-clinical studies that take approximately three years (PAREXEL, 2004: 183) in a prospect of obtaining $5 m cash flow and another $580 m at the end of the following seven years if the drug against tuberculosis is developed. If such a drug is not developed, the Program pays only the first payment ($5 m), POC costs (*P*) are assumed at $2 m, and clinical trials costs (about $10 m) and some overhead costs of about $0.5 m, which add up to about $17.5 m in case of

the very promising drug candidate failure at the end of phase III trials. The Program

shares risks, which ought to be paid.

The Program can choose a complementary portfolio of drug candidates to increase

the rate of success. Let us consider a simple case of *n* independent candidates with

individual success rate *q*, which is the Bernoulli distribution with an expected number of

successful drugs *nq* and variance *nq(1-q)*. If the Program wants to reduce its overall

failure rate with such *n* drug candidates to less than α; the probability of failure for *n*

independent trials would be $(1-q)^n \leq 0.05 \rightarrow n \geq log(\alpha)/log(1-q)$. Given a standard α=0.05,

i.e. achieving the Program's success with a 95% confidence, *q* can be estimated by

assuming that one in five of compounds entering clinical trials will be successful. Table

1 shows the expected costs of the Program.

Table 1. Expected costs of the Program for tuberculosis in year 2000 prices, US$

Probability of individual drug candidate success, *q*	Minimum number of drug candidates to reduce the Program failure to less than 5%, $n \geq log(\alpha)/ log(1-q)$	Expected number of successful drugs, *nq*	Expected costs of the Program, $, *[n(F+C+P)+ S*nq]*1.2*	Expected costs per successful drug: expected costs of the Program divided by *nq*	Expected costs with only one successful drug (if more than 95% failure rate), *[n(F+C+P)+ S]*1.2*
0.1	29	2.9	2610.0	900.0	1287.6
0.15	19	2.85	2371.2	832.0	1083.6
0.2	14	2.8	2234.4	798.0	981.6
0.25	11	2.75	2138.4	777.6	920.4
0.3	9	2.7	2062.8	764.0	879.6
0.35	7	2.45	1848.0	754.3	838.8
0.4	6	2.4	1792.8	747.0	818.4

Note: assuming Bernoulli distribution, the second payment S=$580mln, the first payment F= $5 m, costs of clinical trials C = $10 m and 20% overhead costs.

Paul, et al (2010: 205) offer an alternative estimation showing that 9 to 11 drug

candidates are needed to enter clinical trials to expect one NME approved, i.e. probability

of successful passing of clinical trials is about 0.12. However, this probability could be too low as a significant share of candidates are dropped due to financial and strategic considerations in commercial R&D (DiMasi, et al, 2004).

The assumed range of probabilities for success in clinical trials (Table 1) corresponds with the rates from 12% to 33.3% for self-originated new chemical entities (DiMasi, 2001:301) for the therapeutic classes of neglected diseases. However, the benchmarking average success rate of 20% is lower than the average success rate for anti-infective drug candidates, which are estimated at 28% by DiMasi.

In general, in 2000 prices for the tuberculosis 2-SPPP is expected to run at an average cost of $800 m and delivering two or three new quality drugs. The proposed Program should deliver at least one new quality drug at a cost of $982 m assuming a 20% success rate in clinical trials for a drug candidate.

5. Conclusion

The proposed scheme focuses on cost-efficient drug discovery only. The estimated costs of the Program for a TB drug are approximately $750-900 m per successful drug in year 2000 prices. These costs of the proposed Program are higher than those of PPPs due to setting relatively high outside commercial option for firms, but essentially lower than the ones estimated for the APC scheme. Given that the proposed Program targets high quality drugs and allocates production licences of new drugs in developing countries into the public domain, this scheme can compete with PPPs, which are considered to be the current best option. The advantages of the proposed 2-SPPP scheme include direct payment for the

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revealed drug quality; prompt publication of the information about performance of all drug candidates, a large reduction of risks and costs for small innovators; and better incorporation of developing country needs.

Potential problems of the proposal include an incentive for firms with sunk R&D costs to overstate the attributes of their drug candidate. The Program management should balance this by a right to contract out some independent tests on key characteristics of a candidate. There could be practical difficulties with accurate cost-benefit analysis of new drugs and it is important to build a consensus methodology for this analysis.

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