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The economics of priority review vouchers

Nicola Dimitri[1,2*], dimitri@unisi.it

Priority review vouchers (PRVs) were introduced in 2007 by the US Congress as an incentive mechanism to spur pharmaceutical firms' R&D efforts for neglected diseases (NDs). A voucher, which a firm can obtain upon approval of a new treatment for NDs, entitles the holder to prioritize the FDA review for any drug. The proposal generated much controversy regarding its ability to effectively stimulate R&D for NDs. Here, after reviewing the main issues of the debate, i use a stylized economic model to discuss the strength of PRVs as an economic incentive to invest in research. My findings suggest that R&D investments might be higher when the developer could prioritize a valuable compound.

Introduction

As an instrument to fight neglected diseases (NDs), particularly tropical infectious and parasitic diseases, on 27 September 2007, the US Congress enacted a law introducing the priority review voucher (PRV) mechanism [1–3]. The Congress decision formalized a proposal made in 2006 [4], aiming to leverage R&D efforts for drugs, vaccines and biologics treating NDs.

The basic functioning of the PRV mechanism is simple. Any new, approved treatment curing one of the diseases specified in the law will be awarded the right to a PRV by the FDA. The voucher entitles the holder to a priority review of any of its own drugs submitted for registration to the FDA. Alternatively, the voucher could be sold to another subject, which, in turn, might use it to prioritize the review of one of its drugs submitted for approval to the FDA [5]. There are no restrictions on the procedure adopted to sell the voucher, which could range from a bilateral negotiation to an auction. Finally, the holder of a voucher can decide to wait and see how the market goes and stock the PRV for some time rather than using it or selling it immediately.

The idea underlying the PRV mechanism is that prioritization can act as an economic incentive: anticipating by 6–12 months [6] the market entrance of a drug can have meaningful economic value. In particular, for a blockbuster drug it has been estimated that such value could be approximately $300 million [4], although some alternative estimates are more conservative [6] and others even higher [7]. The potential returns generated by review prioritization, therefore, should stimulate firms to invest in R&D for drugs treating NDs. It is this link between the R&D effort for NDs and the market for drugs treating non-NDs that should make PRVs act as a pull economic incentive [8]. It is still too soon to say whether such a link will be successful because, so far, only one PRV has been awarded – to Novartis in 2009, for the *Coartem* treatment of malaria – and no use or sale of it has been made yet.

Despite the underlying motivation, the proposal caused controversy [9–12] regarding whether it could be an appropriate economic instrument to tackle the issue. Among others, drug safety and distortion in resource allocation and in already established review lists of non-ND treatments submitted for registration have been of particular concern.

The debate on PRVs has been hosted in a variety of sources, from academic and policy journals to reports and documents. Yet, despite such rich confrontation and discussion, to my knowledge it still seems to be missing a more systematic investigation toward a better understanding regarding whether, and to what extent, PRVs can ultimately stimulate higher R&D investments for NDs.

On the basis of the above considerations, my main goal is to contribute to further insights on the economics of PRVs. Indeed, after a brief

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.08.008

review and summary of the fundamentals of the mechanism and the main issues at stake in the related debate, within a stylized economic model i attempt to shed light on whether PRVs can effectively spur R&D efforts for treatments curing NDs. It is worth anticipating that my findings suggest how the incentive to invest could be stronger when the developer of a drug qualifying for a PRV has a portfolio that includes other potentially very profitable compounds treating non-NDs.

The PRV mechanism

Human drugs, vaccines or biologics, submitted for registration after the law enactment [1], approved by the FDA and improving upon the existing ones on prevention, detection or treatment, are entitled to PRV if they concern the following tropical diseases: '(A) Tuberculosis, (B) Malaria, (C) Blinding Trachoma, (D) Buruli Ulcer, (E) Cholera, (F) Dengue/Dengue Haemorrhagic Fever, (G) Drancunculiasis (Guinea-Worm Disease), (H) Fascicoliasis, (I) Human African Trypanosomiasis, (J) Leishmaniasis, (K) Leprosy, (L) Lymphatic Filariasis, (M) Onchocercasis, (N) Schistosomiasis, (O) Oil Transmitted Helmitiasis, (P) Yaws, (Q) Any other infectious disease for which there is no significant market in developed nations and that disproportionately affect poor and marginalized populations, designated by regulation by the Secretary'.

The holder of a PRV must notify the FDA, no later than 365 days in advance, of its intention to prioritize the review of a specified drug. Advanced notification will be used by the FDA to properly organize the faster review, although there is concern as to whether one year will be enough [5,6]. Notification also implies that the holder commits to pay a fee to the FDA, fixed on a case-by-case basis and used by the FDA to cover the extra costs needed for the faster validation track, without affecting the resources available for all other reviews. From the point of view of the applicant, the debate raised a further issue concerning a possible mismatch between the average length of time needed to complete phase III and the one year in advance notification [6].

PRVs as economic incentives

The PRV is a form of pull incentive because it generates revenue only upon successful drug discovery; however, with respect to other types of pull incentives (such as Advanced Market Commitment), with PRVs there is typically higher uncertainty concerning future returns from R&D investments, as well as their amount. Indeed, besides the uncertainty intrinsic to successful drug discovery, PRVs can generate returns if they are either sold on the market or used for priority review of another drug in the portfolio of the holder. In the former case, however, it would be difficult to know beforehand the value of the voucher because this depends upon several factors, such as the general economic situation when the voucher will be available, the therapeutic area where priority review will be used and the number of circulating PRVs – all elements that would be difficult to know precisely at the time when the decision to invest in R&D is taken.

Moreover, the returns coming from prioritizing a chosen drug already in the portfolio can be uncertain. Indeed, the bearer would not necessarily know if and when there would be a potentially profitable drug in its portfolio worth prioritizing.

Finally, PRVs as incentives could be subject to the following, somewhat paradoxical, consideration. The more successful the program is, the higher the number of PRVs awarded by the FDA will be and the lower their economic value will tend to be, weakening PRVs as an incentive in spurring R&D for NDs. Indeed, for PRVs to operate effectively their potential value should not fall below a certain threshold and the number of PRV circulating at any one time should be limited.

Some controversial issues with PRVs

In this section, i summarize some of the main crucial issues concerning the proposal. The first point relates to the principle inspiring the mechanism. Although it was contemplated in the initial suggestion by Ridley *et al.* [4], to award a PRV the law does not seem to require the sponsor to have found a manufacturer for the new treatment for ND. Hence, although the economic value of a PRV can stimulate the development of new drugs, it could be that such drugs would still not reach the affected population because no manufacturer is willing to produce them. Should this be so, despite having induced the availability of a new treatment for ND, the very goal of the program would be missed.

A further issue concerns drug safety under accelerated procedures [9,10,13–17], although opinions differ on whether priority review implies acceleration [18]. Moreover, doubts have been raised over whether this would be a strong enough instrument to induce large pharmaceutical firms to undertake R&D for NDs that, because of the lack of potential market, they were not interested in before the enactment of the PRV law. For this reason, there seems to be a shared sentiment [5,6,9,10] that PRVs will probably stimulate R&D efforts by dedicated non-profit organizations, such as Public-Private Partnerships, that could use the PRV revenues to support the manufacturing of the approved drug or by small biotechs with expertise already built in the area that could use the PRV returns as a source of funding.

Having summarized the main features of the mechanism and related debate, in the next section i introduce the economic model on which i base my economic analysis. I shall evaluate the role of PRVs as economic incentives by comparing the R&D effort levels in the model without, and with, PRVs.

The model without PRVs

Consider a firm having a portfolio made of two compounds, α and β, with associated future profits given, respectively, by Π_α and Π_β. In what follows, i shall assume project α to be the one eligible for a PRV and, to simplify the exposition, that project β could not be considered for priority review without a voucher [6].

As simple as it could be, this setting is rich enough to gain some main insights. Moreover, let r_α and r_β indicate the R&D investment levels in the two projects and $p(r_\alpha)$ and $p(r_\beta)$ their probabilities of successful drug discovery and registration. I assume success probabilities to be such that $p'(r_\alpha) > 0$, $q'(r_\beta) > 0$, $p''(r_\alpha) < 0$, $q''(r_\beta) < 0$ and $Lim_{r_\alpha \to \infty} p(r_\alpha) = 1 = Lim_{r_\beta \to \infty} q(r_\beta)$, to formalize the idea that in both projects the likelihood of discovery and registration increases with the R&D investment level, although at decreasing rates, and that uncertainty can only be eliminated with an 'infinite' amount of R&D effort.

Finally, i assume the two development processes to be stochastically independent so that the probabilities of joint events are obtained by multiplying the marginal probabilities. Moreover, because probabilities depend only upon one R&D investment level, i exclude the presence of 'externalities', whether positive or negative, between the two drug discovery processes.

Although these assumptions do not cover all possible situations, they still seem to capture a good generality of cases. Moreover, assuming decreasing rates of growth for the success probabilities would also translate into considering the least favorable situation for PRVs to stimulate R&D for NDs. Indeed, assuming constant or increasing rates of growth would introduce a much stronger incentive for such investments. Therefore, my findings on R&D effort levels will be reinforced when considering more favorable situations. Finally, the company

has an overall budget, B, allocated to R&D, but with no major loss of generality, i shall assume that B will always be high enough to cover the chosen R&D investment levels, namely $r_\alpha + r_\beta \leq B$.

The optimal R&D investment for the portfolio

When PRVs are not available, the firm portfolio profits $\Pi(r_\alpha, r_\beta)$ are given by

$$\Pi(r_\alpha, r_\beta) = \begin{cases} \Pi_\alpha + \Pi_\beta - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta) \\ \Pi_\alpha - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)(1 - q(r_\beta)) \\ \Pi_\beta - r_\alpha - r_\beta & \text{with probability } (1 - p(r_\alpha))q(r_\beta) \\ -r_\alpha - r_\beta & \text{with probability } (1 - p(r_\alpha))(1 - q(r_\beta)) \end{cases}$$

Assuming the firm to pursue expected profit maximization, the R&D investment levels maximizing the firm expected profit $E\Pi(r_\alpha, r_\beta)$ is obtained by solving the following problem:

$$\begin{aligned} &\mathrm{Max}_{r_\alpha, r_\beta} E\Pi(r_\alpha, r_\beta) \\ &= \mathrm{Max}_{r_\alpha, r_\beta}[p(r_\alpha)q(r_\beta)(\Pi_\alpha + \Pi_\beta) \\ &\quad + \Pi_\alpha p(r_\alpha)(1 - q(r_\beta)) \\ &\quad + \Pi_\beta q(r_\beta)(1 - p(r_\alpha)) - r_\alpha - r_\beta] \end{aligned} \quad (1)$$

which, rearranging terms, becomes

$$\begin{aligned} &\mathrm{Max}_{r_\alpha, r_\beta} E\Pi(r_\alpha, r_\beta) \\ &= \mathrm{Max}_{r_\alpha, r_\beta}[p(r_\alpha)\Pi_\alpha + q(r_\beta)\Pi_\beta - r_\alpha - r_\beta] \end{aligned} \quad (2)$$

The above shows that because the two projects are independent, the optimal R&D solutions for the portfolio coincide with the optimal solutions of the two projects taken separately.

Given the assumptions on success probabilities, the firm would find it profitable to invest a positive amount of resources in project α if $p'(0)\Pi_\alpha > 1$ and in project β if $q'(0)\Pi_\beta > 1$.

Having supposed that project α is the one qualifying for PRV, if $p'(0)\Pi_\alpha < 1$ then no R&D investment would be made in such project and the related disease be neglected.

Assume instead that both conditions for positive investment are met, the optimal R&D effort levels for the two projects solve the following (first-order) optimality conditions.

$$p'(r_\alpha) = \frac{1}{\Pi_\alpha}; \quad (3a)$$

$$q'(r_\beta) = \frac{1}{\Pi_\beta} \quad (3b)$$

It is worth noticing that the assumptions behind $p(r_\alpha)$ and $q(r_\beta)$, as well as the form of the expected profit, guarantee that the first-order conditions (3a) and (3b) identify the positive R&D solutions to (2). With the same assumptions on probabilities, but a different expected profits formulation, first order conditions may not necessarily characterize the optimal solutions. Again, to simplify the exposition (without losing much generality, however), throughout the article i shall assume that the first-order conditions identify the expected profit-maximizing positive solutions.

For an illustration of the above analysis, consider $p(r_\alpha) = 1 - e^{-ar_\alpha}$ and $q(r_\beta) = 1 - e^{-br_\beta}$.

Because these two functional forms are the same, in this simple case the intrinsic difficulty of the two drug discovery projects is formalized only by the parameters a and b. In particular, the higher their value, the easier the discovery is. And, indeed, conditions for positive R&D investments in project α and β are given, respectively, by $a > (1/\Pi_\alpha)$ and $b > (1/\Pi_\beta)$. Assuming they are met, (3a) and (3b) now become

$$ae^{-ar_\alpha} = \frac{1}{\Pi_\alpha}; \quad (4a)$$

$$be^{-br_\beta} = \frac{1}{\Pi_\beta} \quad (4b)$$

from which, as optimal R&D investment levels, i obtain $r_\alpha = (\log(a\,\Pi_\alpha)/a)$ and $r_\beta = (\log(b\,\Pi_\beta)/b)$, which, in fact, are positive when the above inequalities hold.

R&D will be higher in project α, namely $r_\alpha > r_\beta$, if $(\log(a\Pi_\alpha)/a) > (\log(b\Pi_\beta)/b)$, hence if $a > ((b\Pi_\beta)^{(a/b)}/\Pi_\alpha)$. To summarize, the example suggests that it is the shape of the success probabilities that determines the relation between the intrinsic difficulty of α and β and their prospective profits, which will define which of the two projects receives a higher amount of R&D resources.

The model with PRVs

Suppose now that PRVs are available; below, i formalize how, in my view, PRVs mainly operate. I have already discussed that PRVs can be meaningful drivers stimulating R&D if they can act as economic incentives (namely, if they can increase the prospective profits of a drug discovery project for infectious diseases). That is, a firm owning a voucher can use it to raise its profits, but whether this could effectively occur – and, if so, to what extent – might be uncertain when the company decides its R&D investment level. More specifically, the economic value of a PRV can come from two possible sources. First, the voucher could be sold to another company, but if it will be sold and at what price might be uncertain *ex ante*. This possibility could also include the case of trading the PRV. Alternatively, the holder can use the voucher to prioritize the review of another compound in its portfolio, as long as there is such compound and if its prioritization can generate additional profits.

In the next section, i introduce PRVs in the model discussed in the previous section and, in a simple way, formalize the two possible channels through which PRVs could increase the firm profits and act as an economic incentive.

PRVs as an incentive to R&D effort for NDs

Having assumed project α to be the one eligible for a PRV, below i formalize its potential economic value.

(i) With no main loss of generality i model the market value of the voucher, and related uncertainty, simply by assuming that it could be sold to another company either at a high price, V_H, with probability $0 \leq \delta \leq 1$, or at a low price, V_L, with probability $(1 - \delta)$, where $V_H > V_L \geq 0$. The case of $V_L = 0$ would capture the possibility of the voucher remaining unsold. Therefore, $EV = \delta V_H + (1 - \delta)V_L > 0$ is the expected market value of the voucher. Notice that these two prices could also be interpreted as the highest and the lowest price, respectively, at which the holder could sell the PRV.

(ii) If not sold to another company, the voucher could be used to prioritize project β, for which the associated profits would increase to $\lambda\Pi_\beta$, with $\lambda > 1$. It follows that prioritizing the review of β would increase the firm profits by $(\lambda - 1)\Pi_\beta$.

To have a proper understanding of how PRVs could operate as economic incentives, in what follows i consider three cases separately: for convenience, (i) will be called external and (ii) internal incentives to be awarded a voucher.

$V_H > V_L \geq (\lambda - 1)\Pi_\beta > 0$

I start with the case of a weak internal incentive, namely a situation in which the additional prospective returns coming from prioritizing project β, already in the holder portfolio, are below the two possible market prices of the voucher. In this case, the firm profits generated by the portfolio of compounds are

$$\Pi(r_\alpha, r_\beta) = \begin{cases} \Pi_\alpha + \Pi_\beta + V_H - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)\delta \\ \Pi_\alpha + \Pi_\beta + V_L - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)(1-\delta) \\ \Pi_\alpha + EV - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)(1-q(r_\beta)) \\ \Pi_\beta - r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))q(r_\beta) \\ -r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))(1-q(r_\beta)) \end{cases}$$

and the optimal R&D effort levels obtained by solving

$$\begin{aligned} &\mathrm{Max}_{r_\alpha, r_\beta} E\Pi(r_\alpha, r_\beta) \\ &= \mathrm{Max}_{r_\alpha, r_\beta}\, p(r_\alpha)[\Pi_\alpha + EV] - q(r_\beta)\Pi_\beta - r_\alpha \\ &\quad - r_\beta \end{aligned} \tag{5}$$

from which the following first-order conditions obtain

$$p'(r_\alpha) = \frac{1}{\Pi_\alpha + EV}; \tag{6a}$$

$$q'(r_\beta) = \frac{1}{\Pi_\beta} \tag{6b}$$

Because EV > 0, from (6a) it follows immediately that with the PRV the R&D investment in project α now, if positive, increases, whereas (6b) coincides with (2b) and so r_β remains unaltered. Intuitively, this is because the internal incentive is dominated by the external incentive, which induces changes only in R&D investment for project α. In this case, the projects remain independent, as when PRVs are not available.

The above consideration, however, does not guarantee positive expected profits in project α, and so a positive r_α if the related disease was neglected before PRVs became available. Indeed, if $p'(0)\Pi_\alpha < 1$, the condition for positive investment would now be $p'(0)(\Pi_\alpha + EV) > 1$, which could only be satisfied if *EV* is high enough (i.e. if the external market incentive is sufficiently strong).

$V_H > (\lambda - 1)\Pi_\beta \geq V_L > 0$

In this case, the internal incentive is not dominated by the external incentive, and the firm prospective profits are now

$$\Pi(r_\alpha, r_\beta) = \begin{cases} \Pi_\alpha + \Pi_\beta + V_H - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)\delta \\ \Pi_\alpha + \lambda\Pi_\beta - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)(1-\delta) \\ \Pi_\alpha + EV - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)(1-q(r_\beta)) \\ \Pi_\beta - r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))q(r_\beta) \\ -r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))(1-q(r_\beta)) \end{cases}$$

so that (5) now becomes

$$\begin{aligned} &\mathrm{Max}_{r_\alpha, r_\beta} E\Pi(r_\alpha, r_\beta) \\ &= \mathrm{Max}_{r_\alpha, r_\beta}\, p(r_\alpha)\{q(r_\beta)(1-\delta)[(\lambda-1)\Pi_\beta \\ &\quad - V_L] + \Pi_\alpha + EV\} + q(r_\beta)\Pi_\beta - r_\alpha - r_\beta \end{aligned} \tag{7}$$

Having assumed first-order conditions to characterize optimality, solutions to (7) are given by

$$p'(r_\alpha) = \frac{1}{p(r_\alpha)(1-\delta)[(\lambda-1)\Pi_\beta - V_L] + \Pi_\alpha + EV}; \tag{8a}$$

$$q'(r_\beta) = \frac{1}{p(r_\alpha)(1-\delta)[(\lambda-1)\Pi_\beta - V_L] + \Pi_\beta} \tag{8b}$$

Because $[(\lambda - 1)\Pi_\beta - V_L] \geq 0$ from (8a) i obtain that r_α solving the equation now is, in general, larger than the solution to (6a). Moreover, for the same reason, the r_β solving (8b) is higher than the one solving (6b).

To summarize, if when neither the internal nor the external incentive dominates, the R&D level in both projects could potentially increase with respect to when the external, market incentive is dominant.

$(\lambda - 1)\Pi_\beta \geq V_H > V_L > 0$

Finally, when the *internal* incentive is the strongest, prospective profits are as follows:

$$\Pi(r_\alpha, r_\beta) = \begin{cases} \Pi_\alpha + \lambda\Pi_\beta - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)\delta \\ \Pi_\alpha + \lambda\Pi_\beta - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)q(r_\beta)(1-\delta) \\ \Pi_\alpha + EV - r_\alpha - r_\beta & \text{with probability } p(r_\alpha)(1-q(r_\beta)) \\ \Pi_\beta - r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))q(r_\beta) \\ -r_\alpha - r_\beta & \text{with probability } (1-p(r_\alpha))(1-q(r_\beta)) \end{cases}$$

and the optimal R&D effort obtained by solving

$$\begin{aligned} &\mathrm{Max}_{r_\alpha, r_\beta} E\Pi(r_\alpha, r_\beta) \\ &= \mathrm{Max}_{r_\alpha, r_\beta}\, p(r_\alpha)\{q(r_\beta)[(\lambda-1)\Pi_\beta - EV] \\ &\quad + \Pi_\alpha + EV\} + q(r_\beta)\Pi_\beta - r_\alpha - r_\beta \end{aligned} \tag{9}$$

With positive R&D effort levels, optimality conditions would now become

$$p'(r_\alpha) = \frac{1}{q(r_\beta)[(\lambda-1)\Pi_\beta - EV] + \Pi_\alpha + EV}; \tag{10a}$$

$$q'(r_\beta) = \frac{1}{p(r_\alpha)[(\lambda-1)\Pi_\beta - EV] + \Pi_\beta} \tag{10b}$$

In this case, too, the solution to both (10a) and (10b) in general contemplates higher R&D effort levels than in (6a) and (6b), the only exception being when $(\lambda - 1)\Pi = V_H$ and δ = 1. Moreover, because $(\lambda - 1)\Pi_\beta \geq V_H$ implies $[(\lambda - 1)\Pi_\beta - EV] \geq (1 - \delta)[(\lambda - 1)\Pi_\beta - V_L]$, it follows that the R&D solution to (10a) and (10b) are in general larger than the solutions to (8a) and (8b).

I summarize the above findings in the following proposition: PRVs tend to increase R&D investment for drugs treating NDs. Such an increase would be larger whenever a firm has as a sufficiently strong internal incentive, as compared to the external, market incentive, to obtain the voucher. When this is so, PRVs will also tend to increase R&D investments for the internal compound prioritized by the voucher, which would not occur when the internal incentive is weak.

Concluding remarks

Within a simple economic model, this article is an endeavor toward a better understanding of how effective PRVs can be as incentives, stimulating R&D investments for drugs treating NDs. The analysis suggests that, under some general conditions, PRVs tend to increase R&D efforts, notably if a firm obtaining a voucher has in its portfolio a particularly valuable compound to prioritize. When this is so the bearer is, in some sense, outperforming the market because the value it can create internally, by prioritizing a drug, is higher than what it could obtain by selling the voucher. Such a finding seems to capture the spirit behind PRV, of linking R&D efforts for NDs with those for non-NDs. As a first attempt to formalize the economics of PRV, the article leaves open to future research few issues. In particular it abstracts from strategic, and asymmetric information, considerations that in more articulated versions of the model might have a role. For example, the strategic use of private information might prevent an efficient exchange from taking place when the bearer assigns a low value to the voucher but tries to sell it at a high price, whereas the interested buyer might assign a high value to the voucher but try to purchase it at a low price.

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Nicola Dimitri [1,2]
[1] *Faculty of Economics, University of Siena, 53100, Italy*
[2] *Visiting Professor IMT Lucca, 55100, Italy*
dimitri@unisi.it