ECONOMIC SUSTAINABILITY OF AN ALTERNATIVE FORM OF INCENTIVIZING PHARMACEUTICAL INNOVATION: THOMAS POGGE'S PROPOSAL

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ABSTRACT: The research and development of new drugs and vaccines is costly. Current economic incentives for pharmaceutical research come from intellectual property policies that grant innovators the exclusive monopoly for marketing their discoveries. The existing patent system does not encourage the development of drugs whose sale would not generate high returns. As a result, little is invested in researching and developing medicines that could cure or prevent rampant disease and death among the poorest segments of the global population, particularly in developing countries. Philosopher Thomas Pogge has recently addressed this problem from an ethical point of view, proposing an alternative reward scheme based on the therapeutic effectiveness of new products.
This paper provides an analytical review of Pogge's reform proposal from an economics perspective. The main question is whether the alternative incentive system is effective enough to promote the discovery of new medicines for neglected diseases. Theoretical models are defined to assess the required reward of pharmaceutical innovation within the framework of Pogge's proposal. The mathematical approach taken is mainly based on the investment under uncertainty concept. Results from the simulations performed indicate that Pogge's scheme may be effective mainly for widespread diseases like malaria and HIV.

Keywords: pharmaceutical innovation, therapeutic efficiency

JEL Codes: H8, I11, I18

Introduction

Pharmaceutical research requires vast financial resources. Intellectual property rights provide the necessary incentives for doing research by providing developers a monopoly over the sales of their new products. Decisions about whether to develop a new drug or vaccine thus depend on the expected revenues from its sale. The unfortunate consequence is that companies have little incentive to develop pharmaceuticals for diseases found mainly in countries with unprofitable markets. Addressing this issue, philosopher Thomas Pogge recently outlined a proposal for incentivizing pharmaceutical innovation that does not rely on monopoly pricing.

This paper presents a model for the quantitative assessment of Pogge's proposal. The model is based on the well-established financial option pricing theory, which has already been adopted by other works evaluating incentives for pharmaceutical research.

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Pogge's Proposal

Under the existing patent system, pharmaceutical companies profit from their research by selling patented drugs at much higher prices than production marginal costs. However, even more problematic than the resulting high prices is the lack of available incentives for developing drugs useful for the treatment and prevention of diseases common mainly in developing countries, where the expected return from the sale of such drugs is low. This has drastically limited research into such drugs. From 2004 to 2008, the sales of new medicines in the United States alones amounted to an astounding 66% of the global total while the rest of the world, not including Europe and Japan, accounted for a mere 5% (EFPIA, 2009).

The problem is also dramatically evident for vaccines. Although proven effective in the prevention of disease and easier to administrate than other drugs, research into vaccines against diseases affecting poor countries remains limited. The situation is similar for drugs used in the therapy of rare diseases, the so-called orphan drugs.

Most critics of the intellectual property system have an academic background in economics. Pogge's approach to the problem (2005) is therefore noteworthy, given his sociological and political background. Pogge calls for careful analysis of alternative proposals to the current incentive system in order to find a better solution. Economics is undeniably important, but it is not enough. Tackling the problems of how to pay for pharmaceutical research and provide access to drugs and health care must take into account the importance of these issues for humanity. One cannot compare research into products that are essential for life with other creative activities leading to non-essential goods or services. Pogge maintains that the conceptual and methodological premises of dealing with the pharmaceutical research issue define an ethical paradigm for assessing the current incentive scheme based on intellectual property.

Starting from these considerations, Pogge condemns the current state of pharmaceutical and health research worldwide - with reference to the needs of less fortunate countries - as a clear example of a human rights violation against the affected peoples. The main responsibility lies with the system of international treaties that discipline the worldwide pharmaceutical market and research incentives according to the principles of intellectual property.

It is interesting to note that Pogge does not call for doing completely away with the current intellectual property system in the pharmaceutical sector. He acknowledges that the moral validity of a reform scheme cannot disregard economic and political realities. Successful implementation of any such project requires being acceptable to governmental authorities, pharmaceutical companies and public opinion at large.

Pogge identifies two possible categories of reform of the current model of incentives. The first includes the familiar differential pricing strategies, such as the discrimination of sale prices and the use of compulsory licensing for essential medicines. However, these solutions are unlikely to succeed. Price arbitrage may discourage pharmaceutical companies from selling drugs at lower prices in less affluent countries. As for compulsory licensing, in wealthy countries governments are often reluctant to enforce it against the will of pharmaceutical corporations. Furthermore, according to TRIPS agreements, compulsory licensing is apparently contemplated only for the internal use of patented resources. Developing countries without local pharmaceutical firms would rather need importing generic and cheap versions of patented drugs. This would require a worldwide supply of generic drugs, commercialized at low prices. However, to create such a market, compulsory licensing should be extended to production of drugs for the exportation.

Pogge is more confident about the possible success of the second category of strategies, which are based on the concept of public good. He identifies three essential elements for a feasible reform

design inspired by this principle. First of all, each new drug that successfully passes the trial phase should be freely accessible as a public utility good. All pharmaceutical companies will be able to produce it without paying license fees to the discoverers. To provide incentives for research, Pogge introduces the second element of the reform: the innovators' right to a new kind of patent. This patent would have a multi-year validity, like the traditional patent, during which time the patent's owner would be remunerated with public funds commensurate with the new drug's contribution to reducing the global burden of disease. Patent-holders would therefore be interested in making their new medicines available to as many individuals as possible, to maximize its beneficial impact on global health. This would encourage the sale of drugs at low prices as well as increasing effort to simplify the administration of drugs to patients in order to improve their effectiveness. Pharmaceutical companies could even actively support the health services of less developed countries to facilitate distribution of their drugs.

The proposal hence contemplates a link between the therapeutic value of new products and the incentives for innovators, as also suggested by Hollis (2005) and later by Love and Hubbard (2007). Hollis and Pogge share many views on this topic. In a later joint work, they outline a detailed proposal for the creation of a Health Impact Fund (HIF) to reward pharmaceutical innovation under the alternative system (Hollis and Pogge, 2008).

The third element of Pogge's proposed reform concerns the identification and allocation of financial resources to support the scheme, as well as how to make the measures acceptable for all of the stakeholders, including governments, the pharmaceutical industry and worldwide public opinion. The wealthiest countries would undoubtedly be the greatest contributors to funding the scheme, but this would not be an exorbitant burden. According to Hollis and Pogge, the initial annual commitment for HIF funding could be as little as 6 billion USD. At this scale, it would be possible to support the development of about two new drugs every year. The fund size is scalable, so it can be enlarged if the system works well.

Pogge provides several arguments that might persuade the citizens of high-income countries to accept the scheme, apart from the moral unacceptability of the current situation. Above all, the sales prices of essential medicines would drastically decrease, making them affordable to poor people all over the world, including those in affluent countries. This would result in redistributive social effects. Another key argument is that less advantaged people might recognize the goodwill of the affluent minority of the global population. This argument would not be very effective in a strictly selfish society, but the strong impulse to innovate under the proposed scheme would certainly have beneficial effects on the economy and on employment in those countries conducting research and development activities. Furthermore, the treatment of diseases in developing countries might prevent the outbreak of epidemics that could easily spread to other parts of the world. Finally, the effort required by the project would promote a better reciprocal understanding worldwide.

Alternative incentive system reward

To assess Pogge's proposal requires that a parameter to express the therapeutic benefits of the medicines be established. One possible parameter is the Quality-Adjusted Life Year, or QALY, which is defined by the number of patient's survival years thanks to the use of a drug with an appropriate weight to express life quality. The weighting coefficient is 1 for each year in perfect health, while lower values are used for years of illness or infirmity, or 0 in case of death.

Another possible unit of measure is the Disability-Adjusted Life Year, or DALY. This concept was first introduced in the 1993 World Development Report (World Bank, 1993). DALYs for a disease correspond to the sum of the years of life lost due to premature mortality and the years of healthy life

lost because of disability. In their work, Hollis and Pogge acknowledge that DALY and QALY concepts are similar although they retain distinct characteristics. QALY would be more representative because it is defined through population-level assessments rather than by groups of public health experts. For the aim of the present study, DALY health measurements are of interest because they are usually adopted by international health organisations. The 2008 WHO report on the global burden of disease (GDB) provided projections of DALYs corresponding to several causes of death (WHO, 2008). Taking into account the infectious disease group only, HIV and malaria accounted for about one third of total DALYs. The worldwide weight of harmful tropical diseases is much less relevant. Infections affecting the lower respiratory tract (mainly bronchitis and pneumonia) outweigh even HIV, but several effective drugs are available to deal with these infections. Discovery of vaccines for HIV/AIDS, malaria, tuberculosis and Dengue fever is often indicated as the research target for the next years[3].

Hollis and Pogge present the main features of the reward system in their work, although they concede that many elements still need to be addressed. With the health fund system, the reward for a new medicine is proportional to the total provided benefits. In Hollis and Pogge's study, therapeutic improvement per patient is defined as the difference between the average impacts of the new medicine and the pre-existent baseline treatment, expressed in QALYs or DALYs. The overall benefit is the product of the total number of patients and the average individual health improvement. Although a crude aggregation, it reveals an important aspect of the reward system. The delivered earnings from two equally effective drugs for different illnesses will be proportional to their respective disease burdens. This situation would incentivize research of new medicines for more widespread illnesses, but it would not encourage the development of effective remedies for more circumscribed diseases. This intrinsic limitation is evident for the so-called orphan diseases, but may also occur for pathologies that are not so rare.

The annual reward to developers is equal to the product of the amount of funds available and the share of worldwide health improvement due to the discovered medicine. Assuming that funding is constant as in Hollis and Pogge's baseline scheme, the annual reward may change in a not deterministic way over the compensation period. This may also occur if the medicine-delivered health benefits remain the same and if no new, better remedy for that disease is discovered. The development of effective products to cure other pathologies may reduce the weight of the contribution of global health improvement due to that medicine, thus lowering the amount of reward to its developer.

Previous considerations show that the definition of health improvement contributions is not trivial. A possible solution is to express each contribution as the product of a medicine's effectiveness coefficient and a disease burden parameter. The former term corresponds to the quality or efficacy of the product discovered and can be given as a per cent value[4]. The definition of the latter term is harder. Distribution of medicines usually requires years to achieve the global coverage of the target population. The profile of the global coverage level can be derived from past experience in worldwide immunization efforts, such as the diphtheria, tetanus and pertussis (DTP3) immunization campaigns.

Drugs and vaccines need different approaches for the evaluation of their therapeutic benefits. A drug is administered only to already sick individuals, while vaccination aims at disease prevention. Furthermore, some drugs succeed in definitively eradicating a disease within a limited period; others

[3] For instance, see the presentation by S. Lee (2007).

[4] It is to be remembered that, at least in medical context, efficacy and effectiveness are not the same thing. The former mainly refers to the patient's healing capability of a medicine in controlled conditions, for instance in the context of a medical trial. The latter indicates the health benefits of the product in the population at large. To assess the therapeutic benefits at a global level, the parameter of interest is effectiveness rather than efficacy, which is more strictly associated to the quality of a medicine.

can improve the life quality of the patients, but require lifelong administration, like the HIV/AIDS anti-retroviral medicines. This implies differences in the resulting definitions of therapeutic improvement.

Hollis and Pogge's proposal does not contemplate a free-of-charge distribution of the new product. The producer will demand a price equal to production and distribution marginal costs. Indeed the developer would be interested in distributing the new product to as many people as possible, to maximize the health benefits and hence its reward. This could lead to selling the medicines at a lower price than the marginal costs or promotion of their distribution in other ways. For instance, the developer could support the local health services in low-income countries by financing upgrades of medical equipment or the training of personnel. These efforts could solve the so-called last mile problem that Hollis and Pogge recognize as critical for the achievement of actual therapeutic improvement from new medicines. Although these measures would introduce additional costs not compensated by the sale price, they are expected to be lower than the current high promotional and advertising expenditures under the traditional patent system.

In the preliminary health fund design by Hollis and Pogge, the reward duration is assumed to be ten years. A period of five years is proposed for registration of new therapeutic uses of existing drugs. The traditional patent lasts at least twenty years, but effective marketing life is shorter if patent registration is done in the first stages of research activity[5]. Several years are usually needed before a new product is developed, tested, authorised by competent health authorities and made available to the market.

The average length of the research and development phases has been calculated by the principal world pharmaceutical industry organisations, i.e., EFPIA in the European Union and PHRMA in the United States. It may require from ten to fifteen years after research commences before a newly discovered drug is marketed (EFPIA, 2009 and PHRMA, 2009). Two main phases are identified. The first is the preclinical phase, which corresponds to the development of a new drug or vaccine for a given disease. The scientists assess the potential therapeutic properties of existing chemical compounds or develop new chemical entities. After having demonstrated the therapeutic action with preliminary experiments, preclinical tests are performed in laboratory conditions and sometimes on animals. Preclinical tests may lead to modifications of the candidate medicine. The overall duration of the preclinical phase is usually between three and six years.

The second phase mainly consists of clinical tests and has three subphases. In the first subphase, the safety for human beings is verified and possible side effects are investigated. The second subphase foresees tests on small groups of actual patients to verify the effectiveness of the product in disease treatment. Finally, in the third subphase, wider-scale tests are performed on patients. The overall duration of the whole clinical testing phase is usually about seven years.

After having successfully passed the clinical tests, marketing and distribution applications can be submitted to the national health authorities. After their approval, the new drug can be commercialised. The developer will expand its facilities for large-scale production to meet market demand.

In Hollis and Pogge's work the health fund should pay the reward to the developer of a new drug after the market approval and according to its therapeutic effectiveness. Therefore, the payoff period would start after registration of the medicine under the fund scheme. The proposal foresees ten years for a new medicine. The payoff amount would depend entirely on yearly evaluations of the drug's therapeutic effectiveness. With the conventional system, if the new product patent has been registered at the beginning of research activities, the exclusivity period could expire less than ten years

[5] Under current intellectual property laws, a supplementary protection certificate (SPC) of five more years may be required to prolong the exclusivity of the patentee.

after market approval. Therefore, the innovator would then have only a few years to sell the medicine in monopolistic conditions. With Pogge's scheme, the innovator would be guaranteed payment for the full period. This will address research efforts towards really breakthrough medicines.

Some assumptions may be made about the amount of investments required for discovery and preclinical research, for clinical trials and for building the production facilities. A WHO review of the main worldwide health issues reported an average cost of 800 million USD for developing a new drug (WHO, 2006). This figure comes from a study by DiMasi et al. (2003). In a later work, DiMasi and Grabowski (2007) found even higher costs for drugs developed by biotechnological firms, up to 1.2 billion USD, but these figures have been questioned. In their studies, DiMasi and his colleagues first evaluate the out-of-pocket expenditure of research, starting from a cost database considering the main pharmaceutical corporations. For clinical trials, the costs are calculated by taking in account the transition probability of each subphase. This delivers an average out-of-pocket cost of clinical phase amounting to about 60 million USD[6]. For the preclinical phase, a similar outlay of the cash amount is assessed. However, to calculate the overall cost of research, the authors convert these figures into capitalised costs and introduce a further correction taking into account the success rate, hence inflating the final results. This approach has been severely criticized. In their evaluations, DiMasi and his colleagues included the cost of using money for drug research rather than other investments, i.e., the opportunity cost of the capital, instead of the actual research expenditure of pharmaceutical firms. Furthermore, the reference data sample seems biased towards the producers of blockbuster drugs, so it is not representative of the development process of therapies for diseases primarily affecting developing countries. Another objection is that DiMasi and his colleagues have not considered the relevant tax deductions foreseen for pharmaceutical research in many countries. By subtracting the opportunity cost of the capital and tax deductions the Office of Technology Advancement (OTA) of the Congress of the United States assesses a much lower figure for total research and development activities, corresponding to 110 million USD[7] (Public Citizen, 2001). The figure is consistent with a 2001 evaluation of the cost of clinical trials conducted by the US Congress, which reported 75 million USD.

Other useful data are available for specific research issues. In their work on investments in AIDS vaccine development, Batson and Ainsworth (2001) indicate a required investment of 20 million USD for basic and preclinical research, while the clinical testing phase would need 40 million USD. Another 100 million USD are said to be necessary for scaling up the manufacturing capacity. Indeed drugs and biopharmaceuticals may present different characteristics and development issues.

Higher costs than those mentioned in Batson and Ainsworth work can be found for building manufacturing plants, too. For instance, in 2009, Sanofi-Aventis started the construction of a new vaccine manufacturing facility in France with an investment of 350 million EUR. Considering that an existing pharmaceutical producer will exploit its available infrastructures as much as possible, the required investment for large-scale production can be estimated between 50 and 500 million USD.

The model

The goal of the present work is to assess the economic sustainability of a pharmaceutical research project under the incentives proposed by Pogge. This requires development of an analytical model considering the specific issues of the innovation process. The model will allow estimation of the expected NPV of the project, discounted back to the beginning of the research process. The innovator

[6] The sum is expressed in US dollars at the purchasing power of year 2000.

[7] The original figure was $65.5 million at the purchasing power of year 1990. In the Public Citizen report it has been inflated to year 2000 values.

will start researching a drug for a specific pathology only if the expected NPV is positive. Pogge's alternative incentives should make it more profitable to develop essential drugs and vaccines than under the conventional patent system.

Defining the model would not be too demanding if all the research-describing parameters were fixed and known, but this is not the case. An important issue is the length of the two research phases, as defined in the previous section. Although typical duration values can be found in the literature, giving a preliminary reference, they do not represent the actual length of the preclinical and clinical phases. Their random variability will affect costs. In real conditions, investments will be continuous over time. Only investments to build or upgrade industrial plants for large-scale production, after the new medicine has been successfully developed, can be considered as fixed. For a constant and known investment time rate, the total money will invested depend on phase length and therefore it, too, will be random. Another relevant issue is the quality of the research outcome or the efficacy of final product. A minimum acceptable quality of a drug or a vaccine may be defined in advance, but the actual efficacy is not known beforehand.

The approach we take for dealing with the aforementioned issues is based on the work by Hsu and Schwartz (2007) about the economic feasibility of an HIV/AIDS vaccine. The model elaborated by the authors is here taken as the main reference for the mathematical characterization of economic aspects of pharmaceutical research with the reward system proposed by Pogge. Uncertainty about each phase duration and costs can be characterised by modelling the latter as stochastic processes. At a constant investment rate, it would be equivalent to use the times to completion as the reference parameters, but use of costs seems more appropriate. Two variables are introduced, namely the expected remaining costs to completion of each phase i.e. $K_1(t)$ and $K_2(t)$. They are the conditional expectations of the residual costs to complete the respective research phases, given the time t, and can be represented as Wiener processes with drift over time. A complete illustration of Wiener or Brownian stochastic processes and related theoretical issues is presented in Karatzas and Shreve (1998). Modelling of investment under uncertainty is extensively treated in Dixit and Pindyck (1994).

In the preclinical phase, they are described by the following relations:

1 $$dK_1(t) = -I_1 \cdot dt + \sigma_1 \cdot dW_1(t) \qquad 0 \le t < \tau_1$$

2 $$dK_2(t) = \sigma_2 \cdot dW_2(t) \qquad 0 \le t < \tau_1$$

In clinical phase only, $K_2(t)$ will be not null. The describing equation is:

3 $$dK_2(t) = -I_2 \cdot dt + \sigma_2 \cdot dW_2(t) \qquad \tau_1 \le t < \tau$$

The terms in the equations have the following meaning:

- τ_1 is the actual completion time of preclinical phase.
- τ_2 is the actual completion time of clinical phase.
- τ is the actual length of the research, given by the sum of τ_1 and τ_2.
- I_1 is preclinical phase nominal investment rate, in money per time units.
- I_2 is clinical phase nominal investment rate, in money per time units.

- σ_1 is the $K_1(t)$ process standard deviation, or volatility of preclinical phase investment.
- σ_2 is the $K_2(t)$ process standard deviation, or volatility of clinical phase investment.
- dW_1 is the $K_1(t)$ process Brownian motion term.
- dW_2 is the $K_2(t)$ process Brownian motion term.

At the beginning of the research process, there is an expectation about preclinical and clinical phase costs, given by the respective investment rates I_1 and I_2 and by the initial assumptions about phase lengths $\tau_1(0)$ and $\tau_2(0)$. All these parameters can be derived from the average data of the industry. It is:

4 $$K_1(0) = I_1 \cdot \tau_1(0)$$

5 $$K_2(0) = I_2 \cdot \tau_2(0)$$

In a fully deterministic context, the $K_1(t)$ and $K_2(t)$ expressions would be:

6 $$K_1(t) = -I_1 \cdot t + K_1(0) \qquad 0 \le t < \tau_1$$

7 $$K_2(t) = -I_2 \cdot (t - \tau_1) + K_2(0) \qquad \tau_1 \le t < \tau$$

It is interesting to observe that stochastic variability of the preclinical phase duration affects not only its own completion cost, but also the expected cost of the clinical phase. This reflects the actual features of pharmaceutical research. However, this also means that Eq. 5 may well represent clinical phase expected cost at the beginning of research, but it is not valid thereafter; hence the relation of Eq. 2 is introduced. It may be said that during the first part of the innovation activities a learning process occurs, improving the innovator's awareness about the effort that will be required in the next phase.

To evaluate expected NPV of the research project at the beginning, the expected completion costs at times corresponding to 0, τ_1 and τ are to be derived. $K_1(0)$ and $K_2(0)$ are known and fixed parameters and $K_1(\tau_1)$ and $K_2(\tau)$ are null by definition because the end of each phase is defined when no further financial effort is required. Therefore, the only parameter to determine is the expected clinical phase cost at its beginning or at the end of preclinical phase, that is $K_2(\tau_1)$. It is a random variable, whose values can be simulated by using the statistical characterisation derived from the probability density functions of phase lengths.

Analogous considerations can be formulated about the quality of the research project. Quality of the final product may be described as a random variable with Beta probability density. However, dependence on the research process features shall be introduced. In Hsu and Schwartz's work, this is achieved by defining the expected quality of final product at time t. It is the expectation about new medicine efficacy at a generic time when research is still in progress, keeping in mind that the actual quality of the product will be observable only at the end:

8 $$Q(t) = E_t\{Q(\tau)\}$$

The expected quality of the final product at a given time is therefore a random variable and it may be described by using a modified Beta probability density function. This function will depend on the earlier quality expectation and phase completion delay in reference to its previously expected duration. As for the remaining completion costs, evaluation of the expected quality is needed only at times 0, τ_1 and τ.

In conclusion, under the previously presented assumptions, the research process will be characterised by the following parameters, representing the state variables of the model:

- $K_1(0)$, $K_2(0)$ and $Q(0)$ at the beginning of preclinical phase.
- τ_1, $K_2(\tau_1)$ and $Q(\tau_1)$ at the end of preclinical phase, or beginning of clinical phase.
- τ and $Q(\tau)$ at the end of clinical phase, or at research completion.

The unknown terms are only τ_1, τ, $K_2(\tau_1)$, $Q(\tau_1)$ and $Q(\tau)$ while $K_1(0)$, $K_2(0)$ and $Q(0)$ can be derived or taken from the available literature data. A possible set of values for the former group parameters can be obtained by simulation from the corresponding probability density functions. The logical steps are:

- A τ_1 value is drawn by simulation with its density function.
- The result is then substituted in the $K_2(\tau_1)$ density function and a $K_2(\tau_1)$ value is drawn.
- τ_1 and $K_2(\tau_1)$ values are substituted in the τ_2 density function and a τ_2 value is drawn.
- Expected values for τ_1 at t = 0 and for τ_2 at t = τ_1 are derived, to evaluate the completion delay terms in the expected final quality density function at the beginning of the two phases.
- $Q(\tau_1)$ is simulated from the corresponding density function, having substituted the previously found values in the mean and variance expressions.
- $Q(\tau)$ is simulated from the corresponding density function, having substituted the previously found values, $Q(\tau_1)$ included, in the mean and variance expressions.

Expected NPV at the beginning of the research process is calculated in a backward evaluation, performed in three steps corresponding to the 0, τ_1 and τ time nodes. At τ it is:

$$\mathbf{9} \qquad v(\tau) = e^{-r_c \cdot \tau_3} \cdot \frac{1}{r} \cdot S_0 \cdot E\{h_d\} \cdot \left[1 - \frac{1}{(1+r)^{N_R}}\right] - \frac{I_3}{r_c} \cdot \left(1 - e^{-r_c \cdot \tau_3}\right)$$

I_3 is the investment rate for the upgrade of industrial plants for large-scale production of the drug. The only non-deterministic element is the reward share for the medicine. All the other parameters are assumed to be known. From the result of Eq. 9 it is possible to define the policy function of the innovator at the end of the clinical phase. It expresses the benefit or lack of benefit of expending further effort to move on to large-scale production and distribution of the new product. In Hsu and Schwartz (2007), it is simply assumed that the innovative firm will go on with scaling up plants if the expected NPV at τ is positive; otherwise, it will cease any related activity. This option to abandon results in defining the project present value at τ as:

10 $$V(\tau) = \Omega[v(\tau)] \cdot v(\tau)$$

Here Ω is a Heaviside-like step function, representing the abandonment policy of the innovator.

Evaluation of expected NPV at τ_1 is more complex. At this time, the final quality of discovered product, or its therapeutic efficacy, is not yet known. It is only possible to have an expectation of it. As a consequence, the expected NPV will correspond to its conditional expectation given the state variables at the end of first phase, namely $K_2(\tau_1)$ and $Q(\tau_1)$. It will be:

11 $$v(\tau_1) = E\left\{ V(\tau) \cdot e^{-r_c \cdot \tau_2} - \int_0^{\tau_2} I_2 \cdot e^{-r_c \cdot t} \cdot dt \;\middle|\; Q(\tau_1), K_2(\tau_1) \right\}$$

The innovator policy function for the option to abandon or continue the project at τ_1 is defined in the same way as at former step. If the conditional expected NPV is positive, the innovator will continue to the clinical phase; otherwise the project will be abandoned. Therefore, the resulting present value at τ_1 can be expressed as follows:

12 $$V(\tau_1) = \Omega[v(\tau_1)] \cdot v(\tau_1)$$

Finally, the expected NPV at the very beginning of the research is to be derived. Its evaluation at the end of the preclinical phase will consist of a conditional expectation given the state variables at time 0, namely $K_1(0)$, $K_2(0)$ and $Q(0)$. Therefore:

13 $$v(0) = E\left\{ V(\tau_1) \cdot e^{-r_c \cdot \tau_1} - \int_0^{\tau_1} I_1 \cdot e^{-r_c \cdot t} \cdot dt \;\middle|\; Q(0), K_1(0), K_2(0) \right\}$$

The innovator will decide to start research only if v(0) is at least positive. Therefore, the policy function is defined as at the other time instants. The present value at the beginning of the research, given the option to abandon, is:

14 $$V(0) = \Omega[v(0)] \cdot v(0)$$

For completeness, it is possible to take into account unpredictable events that are not directly related to the research process but that could negatively affect it, such as the occurrence of financial difficulties for the innovating entity, causing a lack of resources for the necessary investments. The modelling of this effect has been performed by Hsu and Schwartz (2007) with reference to a former work by Brennan and Schwartz (1985) about the evaluation of investments in natural resources. Unpredictable events may be described as independent Poisson processes. They can be represented in the model by introducing two increases of discount rate in the two phases. Therefore Eq. 11 and 13 will be updated as follows:

15 $$v(\tau_1) = E\left\{ V(\tau) \cdot e^{-(r_c + \lambda_2)\tau_2} - \int_0^{\tau_2} I_2 \cdot e^{-(r_c + \lambda_2)t} \cdot dt \;\middle|\; Q(\tau_1), K_2(\tau_1) \right\}$$

16 $$v(0) = E\left\{ V(\tau_1) \cdot e^{-(r_c+\lambda_1)\tau_1} - \int_0^{\tau_1} I_1 \cdot e^{-(r_c+\lambda_1)t} \cdot dt \;\middle|\; Q(0), K_1(0), K_2(0) \right\}$$

In expressions λ_1 and λ_2 are the intensities of Poisson processes describing the unexpected damaging events during the two phases.

The main criticality of the illustrated backward evaluation method is that the analytical solution is not feasible. The condition that expected NPV at the end of clinical phase must be positive in order to go on with the production phase would allow putting a constraint on the reward share expected value, and hence on the product quality. However, a closed form solution cannot be derived in correspondence to the end of first phase, because of the conditional expectation dependence on random state variables. Hsu and Schwartz (2007) proposed a numerical approach solution to the problem, based on the algorithm for the estimation of the American option value by Longstaff and Schwartz (2001). Basically, simulations giving state variables are to be done on a large scale. Each group of resulting values identifies a path, characterised by 0, τ_1 and τ time nodes. Of course for each path τ_1 and τ_2 may have different values because of their definition as random variables. For the same reason, the expected final product quality at τ_1 and τ_2 may not be the same at different paths. Only at the 0 time node will it have a known value corresponding to the analysis starting assumption. The expected NPV at research end time in the j_{th} path, indicated as τ^j, is defined as:

17 $$v(\tau^j) = e^{-r_c \cdot \tau_3} \cdot \frac{1}{r} \cdot S_0 \cdot E\{h_d[Q(\tau^j)]\} \cdot \left[1 - \frac{1}{(1+r)^{N_R}} \right] - \frac{I_3}{r_c} \cdot \left(1 - e^{-r_c \cdot \tau_3} \right)$$

In the expression, the dependence of the new medicine reward share on product quality at τ^j is evidenced, but other terms are the same as in Eq. 9. Accordingly, it will be:

18 $$V(\tau^j) = \Omega[v(\tau^j)] \cdot v(\tau^j)$$

At the end of preclinical phase, point estimates of the expected NPV of Eq. 11 for all paths are then derived. To this aim, the simulated values of τ_2 and results of Eq. 18 are used. For the generic j_{th} path the point estimate will be:

19 $$\tilde{v}(\tau_1^j) = V(\tau^j) \cdot e^{-(r_c+\lambda_2)\tau_2^j} - \int_0^{\tau_2^j} I_2 \cdot e^{-(r_c+\lambda_2)t} \cdot dt$$

Point estimates for all the simulation paths shall be regressed onto a set of basis functions. In the current analysis state variables to consider are $Q(\tau_1^j)$ and $K_2(\tau_1^j)$. With the appropriate notation and by normalising the arguments of the functions to the initial assumptions about clinical phase investment and final product quality, it will be:

20 $$\hat{v}[Q(\tau_1^j), K_2(\tau_1^j)] \approx$$

$$\approx \sum_{k=0}^{M'-1}\{\alpha_k \cdot L_k[K_2(\tau_1^j)/K_2(0)] + \alpha_{k+M'} \cdot L_k[Q(\tau_1^j)/Q(0)]\} +$$
$$+ \sum_{p=1}^{2}\sum_{q=1}^{2} \alpha_{2\cdot M'+2\cdot p+q-3} \cdot L_p[K_2(\tau_1^j)/K_2(0)] \cdot L_q[Q(\tau_1^j)/Q(0)]$$

With the proposed set of basis functions the row of A_1 matrix corresponding to the generic j_{th} path will be:

21 $$(A_1)_j = \begin{pmatrix} L_0[K_2(\tau_1^j)/K_2(0)] \\ \dots \\ L_{M'-1}[K_2(\tau_1^j)/K_2(0)] \\ L_0[Q(\tau_1^j)/Q(0)] \\ \dots \\ L_{M'-1}[Q(\tau_1^j)/Q(0)] \\ L_1[K_2(\tau_1^j)/K_2(0)] \cdot L_1[Q(\tau_1^j)/Q(0)] \\ \dots \\ L_2[K_2(\tau_1^j)/K_2(0)] \cdot L_2[Q(\tau_1^j)/Q(0)] \end{pmatrix}^T$$

Previous results allow an approximation of abandonment policy function to be derived at the end of the preclinical phase:

22 $$\Omega[v(\tau_1^j)] \approx \Omega\{\hat{v}[Q(\tau_1^j), K_2(\tau_1^j)]\}$$

Thus the present value of the project at that time node given the option to abandon, for the generic j_{th} path, is:

23 $$\hat{V}(\tau_1^j) = \Omega\{\hat{v}[Q(\tau_1^j), K_2(\tau_1^j)]\} \cdot \hat{v}[Q(\tau_1^j), K_2(\tau_1^j)]$$

Going backward, to evaluate the policy function at the beginning of the research, the point estimate of expected NPV is required[8]:

24 $$\tilde{v}(\tau_0^j) = \hat{V}(\tau_1^j) \cdot e^{-(r_c+\lambda_1)\tau_1^j} - \int_0^{\tau_1^j} I_1 \cdot e^{-(r_c+\lambda_1)t} \cdot dt$$

This is the point estimate for the generic j_{th} path. However, the initial time node τ_0^j is equal to 0 for all the simulated paths. Therefore, the regression technique at this node reduces to approximate the expected present value to the arithmetic mean of the expressions of Eq. 24 for all the paths:

[8] Use of τ_0^j to indicate initial time node stresses that point estimates are expected to be different for each path, although time node instant has the same value i.e. 0 for all of them.

25 $$\hat{v}(0) = \frac{1}{N} \cdot \sum_{j=0}^{N-1} \tilde{v}(\tau_0^j)$$

The policy function is simply the following:

26 $$\Omega[v(0)] \approx \Omega[\hat{v}(0)]$$

Having defined the abandonment policy functions at all time nodes it is now possible to evaluate the expected NPV of the pharmaceutical research project by applying the Monte Carlo method to results from previous simulations. Therefore, the project expected value driving the innovator's decision whether to start the research or not is:

27 $$V(0) = \Omega[\hat{v}(0)] \cdot \frac{1}{N} \cdot \sum_{j=0}^{N-1} \left\{ \Omega\{\hat{v}[Q(\tau_1^j), K_2(\tau_1^j)]\} \cdot \left[V(\tau^j) \cdot e^{-(r_c+\lambda_2)\cdot\tau_2^j} + \right.\right.$$
$$\left.\left. - \int_0^{\tau_2^j} I_2 \cdot e^{-(r_c+\lambda_2)\cdot t} \cdot dt \right] \cdot e^{-(r_c+\lambda_1)\cdot\tau_1^j} - \int_0^{\tau_1^j} I_1 \cdot e^{-(r_c+\lambda_1)\cdot t} \cdot dt \right\}$$

Numerical examples

Simulations have been performed by applying the model to four different cases. The first two take into account the development of a drug, aimed at healing people with a particular disease. Pogge's incentive system results are derived for a widespread disease (like malaria) and for a less widespread but still harmful disease (like Dengue fever). In the latter two cases, the new drug is a vaccine, so evaluations are done by considering the benefits of immunization of still healthy people. The health fund is supposed to have an annual endowment of 6 billion Euros. It is assumed that discovered medicines for only some global spread diseases are rewarded. Specifically, tuberculosis, HIV, malaria and Dengue fever are taken in account.

For an at least preliminary characterisation of the therapeutic improvement due to new products the average disease burden per capita can be estimated, considering the available data about GDB and global diffusion. Simulations with the analytical model require the definition of several parameters. Reward period is assumed to be ten years. Nominal durations of research phases and production plant upgrade and investment rates are derived from pharmaceutical industry typical values. Parameters like the investment volatilities or the final quality delay terms come from the works of Hsu and Schwartz (2007).

The values of two projects to develop drugs for malaria and Dengue fever have been calculated by applying the model. The same time pattern distribution is assumed for all the fund rewarded medicines. Annual reference values of disease burdens are assumed to be proportional to GDB values so the latter can be used in the formula.

For each project, simulation of 10,000 evolution paths of research activities was performed. Malaria has the higher GDB so it is reasonable to expect that it will correspond to the more rewarding project. The project value at the beginning, evaluated according to Eq. 27, was € 7,841 M. Therefore the innovator will undoubtedly find it worthwhile to undertake the research of a new anti-malaria drug.

The situation changes for Dengue fever. Although rare, it is still common worldwide and may degenerate towards serious complications. By applying Eq. 27, the expected NPV at project beginning results equal to € 6.43 M, considerably lower than the resulting value for malaria.

To induce a pharmaceutical corporation or research institute to take the long and expensive path towards discovering a new medicine, a weakly positive estimated NPV is not enough. It is difficult to establish a less trivial reference threshold than the null value. In any case, previous results confirm that development of a new drug for the disease having a larger GDB is much more rewarding.

Pogge's system effectiveness for vaccines can be tested by using evidence from existing studies on future product development. For HIV, malaria and tuberculosis, global coverage progression can be modelled according to demand forecasts from the literature. Unfortunately, no comparable data are available for Dengue fever, so global coverage of a new vaccine for that disease is assumed to follow the DTP3 immunization time pattern, which has as its annual infant surviving cohort 130 million people as the worldwide target population.

As in the previous paragraph, incentives to develop new vaccines for malaria and Dengue fever were considered. Simulation of 10,000 evolution paths was performed for both diseases. The expected NPV at the beginning of the project was estimated by applying Eq. 27 and resulted as € 373.5 M. Instead, the expected NPV for a Dengue vaccine was € 238.3 M. Although lower than the malaria vaccine value, the results are fairly similar. This outcome is plausible, considering that the supposed health benefit profiles for the two vaccines have fairly similar values over the reward period.

Conclusions

The inadequacy of the current patent system to promote the development of new medicines for diseases mainly affecting low-income countries is widely acknowledged. Consequently, reform is being demanded from many quarters. By conceiving of the alternative system as a complement to rather than as substitute of the existing system, Pogge is confident that the main corporate stakeholders of the pharmaceutical market will contribute to its success. While definition of the reward system needs further clarification, Pogge's scheme shows worthwhile potential and merits further analysis.

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Acronyms

AIDS	Acquired Immune Deficiency Syndrome
CHOICE	CHOosing Interventions that are Cost Effective
DALY	Disability-adjusted Life Years
DTP3	Diphtheria-Tetanus-Pertussis
EFPIA	European Federation of Pharmaceutical Industries and Associations
GAVI	Global Alliance for Vaccines and Immunization
GDB	Global Disease Burden
HIF	Health Impact Fund
HIV	Human Immunodeficiency Virus
NPV	Net Present Value
OTA	Office of Technology Advancement
PHRMA	Pharmaceutical Research and Manufacturers of America
QALY	Quality-adjusted Life Years
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UNAIDS	United Nations AIDS
USD	United States Dollar
WHO	World Health Organisation