Economic sustainability of an alternative form of incentives to pharmaceutical innovation

*The proposal of Thomas W. Pogge*

Franco Amisano and Alberto Cassone
ECONOMIC SUSTAINABILITY OF AN ALTERNATIVE FORM OF INCENTIVES TO PHARMACEUTICAL INNOVATION
THE PROPOSAL OF THOMAS W. POGGE

Authors:
Franco Amisano, POLIS, University of Piemonte Orientale
Alberto Cassone, POLIS, University of Piemonte Orientale
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Abstract

Research and development of new drugs and vaccines is a complex and expensive activity. Developing a new medicine needs huge investments, from preliminary investigation of active principles to market approval. Current economic incentives to pharmaceutical research come from intellectual property laws, giving a monopolistic position for the marketing of new discoveries to the innovators. However, traditional patent system does not encourage the development of medicines whose sale would not deliver enough high earnings. This situation especially harms the search of remedies to diseases affecting developing countries. Thomas Pogge has proposed an original solution to the problem. Starting from an ethical approach to the issue he has suggested an alternative incentive system based on the therapeutic effectiveness of the new products. Reward would be proportional to the health improvement contribution due to the new medicines that would be sold at a price close to production marginal cost. Required financial resources for reward would be collected at international level, mainly by affluent countries. In a later work Pogge and Aidan Hollis have proposed a scheme contemplating a health international fund for the administration of the system. The peculiarity of the proposal is that it does not invoke the abolition of current patent system. Traditional patents would coexist with the alternative solution and would be the preferred option for the developers of drugs with large and affluent potential markets.

Current work examines the proposal of Pogge primarily from an economic point of view. The key issue is whether the alternative incentive system is enough effective to promote the discovery of new medicines for the neglected diseases, considering the high development costs. To calculate the reward of pharmaceutical innovation in the frame of the alternative system a theoretical model has been defined. The approach is mainly based on the investment under uncertainty concept. Specifically, the model derives from that proposed by Longstaff and Schwartz to estimate the value of financial American options and subsequently adopted by Hsu and Schwartz in their work about the assessment of economic convenience of vaccine research, in the frame of traditional patent system. As usual, pharmaceutical research activities may be divided in two distinct phases. The former includes the preliminary research of active principles that may cure a specific illness and preclinical development and testing of candidate products. The latter mainly consists of clinical trials, leading to the individuation of an effective product. For both the phases uncertainty in the time and cost to completion and in the quality of the final product, corresponding to its therapeutic effectiveness, are considered. Furthermore, expected reward from the health international fund also depends on the eventual concurrent discovery of new remedies for other diseases, affecting the share of resources available to the product developer. Simulations have been done, showing that the solution proposed by Pogge may be effective for largely spread or harmful diseases, like malaria and HIV. However, problems may arise for diseases that are not very diffuse, at least with health fund design as proposed by Hollis and Pogge.
Introduction

Research and development activities in pharmaceutical sector need conspicuous financial resources. In private industry research funding comes from the revenues of pharmaceutical corporations selling their products in temporary monopoly conditions. This occurs because of the acknowledgment of intellectual property rights on the newly developed pharmaceutical products, granting to the industrial developers the market exclusivity on their production and commercialisation. Of course public funded or direct governmental performed pharmaceutical research still has a relevant weight. However, nowadays the role of the private sector in developing new drugs is fundamental. Indeed international treatises on intellectual property have confirmed this situation in several occasions. In particular, the TRIPS agreements have regulated the intellectual property protection at world level, acknowledging its importance as the key instrument to support innovation.

Nevertheless, pharmaceutical research incentives based on intellectual property have serious limits. First of all, they attribute a monopolistic position to the producers of new medicines, with all the typical inefficiencies from supply side. At monopoly price the demand is always lower than in a competitive market. This difference is specifically relevant in pharmaceutical markets, because the production of drugs has generally very low marginal costs. However, main problems arise from the market intrinsic characteristics. Pharmaceutical demand is very heterogeneous around the globe. In high-income countries most of the more common pathologies are not infective. Paradoxically, some of them come from the advanced economic and social development, like the cardiac diseases and other pathologies due to a too rich and unbalanced diet. There is also a high demand of pharmaceutical products that are not essential but contribute to improve the quality of life. In poor countries a deeply different situation exists. Several infective diseases have not yet been defeated and kill many individuals each year. The discovery of drugs for eliminating or curing such pathologies would benefit millions people. Unfortunately, in the current intellectual property regime the choice of pharmaceutical industry to perform research and development activities for these remedies depends on the expected revenues from their sales. For the diseases affecting less affluent countries the potential markets are too poor to provide enough high revenues to cover the predictable development expenditures. Therefore the discovery of remedies
to the main pathologies in the poorest areas of the globe amounts to an intolerably low fraction of
all the pharmaceutical patents.

The ethical unacceptability of this situation has been frequently remarked. In particular, it is
worthwhile to consider the work of Thomas W. Pogge, author of many essays in political
philosophy. The writer has criticized the existing situation from the point of view of human rights.
Monopolistic position conferred to pharmaceutical firms by intellectual property rights would
 correspond to an economic and marketing regime violating the fundamental rights of a great part
of the humankind. Pogge has not limited his analysis to the critics and has formulated an
alternative proposal to promote the pharmaceutical research without recurring to the traditional
monopolistic incentives. It would also avoid the distortion of research and development activities
determined by current system.

The review of the proposal of Pogge is the subject of the present study. It has the goal of
articulating an economic analysis of the author’s solution, to evaluate main issues and advantages
with respect to the traditional pharmaceutical patent system and other alternative formulas to
encourage the research in such sector.

In Section 1 the proposal of Pogge is synthetically illustrated. Ineffectiveness of existing market
incentives to support the finding of new drugs for diseases with prevalent diffusion in developing
countries or affecting small groups is addressed. Specific attention is then put onto the concept of
an alternative solution, intended as complementary and not substitutive of the traditional patent
system, although remedying to its main defects. The review also reports the open issues and
potential flaws of the proposal. For instance, the scheme would better fit to promote
pharmaceutical research for largely diffused pathologies rather than for rare diseases.

The premise for the analysis of the economic sustainability of the proposal is the definition of the
reward to the developer of a new medicine with the parallel incentive system. Other important
elements are the average duration and cost of pharmaceutical research activities and industrial
investments for medicine large scale production and distribution, to provide preliminary
references for the analysis. These issues are illustrated in Section 2.

Section 3 presents the theoretical model to evaluate the amount of incentives required for
effectively promoting the pharmaceutical research in the frame of the parallel system. The key
issue is to assess if the expected revenues from the development of a new drug can pay the
research and development costs. Considering that in the scheme of Pogge the reward depends on
the health benefits of new products, this may be a critical aspect in some cases. Basically, the approach is based on the concept of investments under uncertainty. The model follows a pattern proposed in the financial option pricing theory and already adopted in other works about the evaluation of pharmaceutical research convenience.

Numerical examples are reported in Section 4, where two situations are presented. In the former, reward with Pogge proposed system is evaluated for a drug, to be administered to patients. In the latter, development of a vaccine is considered, for preventive immunization of people at risk. In both the situations evaluations are done for a largely spread disease, like malaria, and a disease with a more limited diffusion.

Section 5 contains some conclusive considerations on the results.

To allow an easier reading of the document, detailed mathematical steps are reported in a final Appendix.
1 Alternative incentives to pharmaceutical research

1.1. The limits of traditional patent system

The acknowledgment of intellectual property rights on their products allow pharmaceutical companies operating in monopoly conditions. In this way they can compensate the research and development efforts by selling patented drugs at much higher prices than production marginal costs. This will limit the access to such products, excluding many subjects with a lower willingness to pay than sale prices.

Nevertheless the existing patent system presents a more critical problem than high prices. The investments for research and development are rewarded with the revenues from the sale of new drugs in monopoly conditions. However, many infective diseases are diffused only in developing countries, mainly in tropical areas. Although sporadic cases may occur in wealthy nations too, they do not represent a health priority for them. Expected returns from the sale of medicines for these pathologies are rather low, because of the limited purchase capability of potential consumers. This situation has severely undermined the industrial research of remedies to such diseases. Indeed, sales of new medicines launched during the period 2004-2008 quite entirely occurred in the markets of developed countries, as shown in Figure 1.1-1. According to data provided by EFPIA the share of sales in the United States alone amounts to an astounding 66%, while the rest of the world, not including Europe and Japan, merely counts for 5% ([1]). Considering that the latter share nowadays includes large emerging nations like Brazil, China and India, new medicines practically had no market in underdeveloped tropical countries, mainly in Africa.

The problem has been evidenced by several authors, like Kremer and Glennerster ([2]). In their work they show that, from 1975 to 1997, only the 0.3 % of the new patented drugs in the world was destined to cure tropical diseases. Therefore market incentives based on current patent system appear inadequate to deal with the medical emergencies of the so-called Third World. This is dramatically evident for the vaccines. They represent an efficient protection against diseases. International campaign for vaccination against smallpox has leaded to its complete eradication within 1980. World Health Organisation (WHO) efforts for joint administration of vaccines against pathologies like yellow fever and measles are providing good results. Vaccines are easier to administrate than other drugs requiring regular assumption for long periods or the involvement of
specialised medical personnel. However, research of vaccines against diseases affecting poor countries remains limited. At the moment there is no effective malaria vaccine. As for HIV vaccine, research efforts have been hitherto mainly devoted to viral subtypes present in wealthy countries. It is not surprising that the international community has sometimes agreed advanced market commitments to improve vaccine research for specific pathologies. However, this is not usually reputed a real alternative solution for promoting pharmaceutical innovation at large, although it allows circumventing the inadequacy of patent system incentives for new vaccines discovery.

An analogous situation is found for drugs used in the therapy of rare diseases. According to European Union criteria a disease is considered rare if it averagely affects not more than 5 subjects on 10,000. Currently known diseases of this kind are about 7,000 so the overall number of patients is not low. However, the returns from the sale of medicines for these pathologies are not expected to cover the huge research and development costs. Indeed, because of the lack of market interest to their development, these medicines are called orphan drugs. To encourage research efforts about them several industrialised nations have introduced dedicated incentives for the pharmaceutical producers, although usually within the frame of conventional patent system.

![Figure 1.1-1: Sales of new drugs launched during period 2004-2008 (Credits: [1])](image-url)
1.2. The proposal of Pogge

Intellectual property system in its current form generally appears unable to incentivize the discovery of medicines for the most diffused pathologies in low income countries. However, its main critics prevalently have an economic academic background. It is therefore noteworthy the approach to the problem by Pogge, for his sociological and political background ([3]).

Pogge remarks the need of a careful analysis of alternative proposals to current incentive system, to find an incontestably better solution. However, notwithstanding the competences of the economists are necessary to this aim, he does not believe they are enough. In an aridly economic perspective there would be no difference between the access to pharmaceutical products and health services and the access to other market goods. Instead the problems of supporting pharmaceutical research and access to drugs and health treatments have to be examined taking in account their importance for the mankind. It is not possible to compare research activities for life essential products and creative activities for the pursuit of not essential goods or services. The author believes that the conceptual and methodological premise to deal with pharmaceutical research issue is the definition of an ethical paradigm for assessing current incentive system based on intellectual property. Each proposal of reform should be evaluated taking in account moral and political issues, together with economic and juridical ones. This is the only way to define an exhaustive and organic reform plan of current system, wholly understandable and assessable by public opinion and political deciders all around the world.

In his analysis of existing situation Pogge starts from the premise that each economic, social or political system should be judged according to its compatibility to human rights, as exhaustively defined in the Universal Declaration of Human Rights of 1948. Each national or international order can be evaluated according to its capability of achieving and enforcing such rights. Their violation usually comes from the voluntary adoption of principles or political choices aimed to neglect them, as in repressive or dictatorial rules. However, human rights can also be violated by social and economic conditions. The Irish Famine of XIX century or the famine due to forced collectivization in Soviet Union in the ‘30 of XX century occurred in deeply different political and institutional contexts. Nevertheless, these events were due to existing economic regimes and could have been avoided, or at least been less tragic, in different conditions. Those economic regimes were per se a
violation of human rights, intended in the general definition issued in the Universal Declaration of 
Human Rights.

Starting from these considerations Pogge writes that current worldwide situation of 
pharmaceutical and health research, with reference to the needs of less fortunate countries, 
represents an evident example of violation of the human rights of affected peoples. The main 
responsibility lies on the system of international and bilateral treaties, crowned by TRIPS 
agreements that have disciplined worldwide pharmaceutical market and research incentives 
according to the principles of intellectual property. This system is not morally defensible, because 
it violates the fundamental right to life and physical wellness of a great part of mankind. A reform 
is therefore indispensable in the name of the restoration and protection of human rights.

A possible objection to these considerations is that TRIPS agreements have been freely subscribed 
by each country. However, it must be remembered that several subscribers could not be qualified 
as democratic, mainly in Africa, and they did not show a great care of possible objections by their 
own citizens. In addition, developing countries could not realistically refuse to subscribe the 
agreements because of the probable economic reprisals at international level. Anyway, their 
acceptance of conditions that probe to be so damaging for their inhabitants cannot be an argument 
to legitimate current incentives to pharmaceutical research. Another remark is that no government, 
although legitimate, should accept measures that damage human rights, because of their 
paradigmatic and universal value. This is specifically true for the international treaties about the 
industrial property of medicines, whose deleterious consequences on the research of new remedies 
mainly affect the children in the least fortunate areas of the globe. This situation is so reprehensible 
that a reform of current incentives to pharmaceutical research is not anymore procrastinable.

It is interesting to note that Pogge does not invoke the abolition of current intellectual property 
system in pharmaceutical sector. Notwithstanding the deep ethical belief that animates his work, 
he acknowledges that moral validity of a reform design cannot disregard economic and political 
realism. Each project shall be acceptable by governmental authorities, pharmaceutical companies 
and public opinion at large to be successfully implemented. It shall then effectively work, 
achieving the wished goals as far as possible without too many faults.

Pogge identifies two possible categories of reform of current model of incentives. The former 
includes the already known differential pricing strategies, like the discrimination of sale prices and 
use of compulsory licensing for indispensable medicines. As shown in previous paragraphs, these
solutions have scarce success probabilities. Instead Pogge is more confident about the strategies based on the concept of public good. The author identifies three essential elements for a feasible reform design inspired by such principle. First of all, each new drug that successfully passes the trial phase shall be freely accessible as a public utility good. All pharmaceutical companies will be able to produce it without paying license fees to the discoverers. This would eliminate the monopoly advantage of developers but also the economic incentives to pharmaceutical research, as foreseen by traditional patent system. To obviate to this problem, Pogge introduces the second element of the reform i.e. the innovators’ right to a new kind of patent. It would have a multi-years validity, like the traditional patent. During this period the patent’s owner would be remunerated with public funds commensurable to the new drug contribution to worldwide morbidity reduction. Therefore each firm that develops a new medical product would be interested in doing it available to as many individuals as possible all around the world, to maximize its beneficial outfalls on the mankind. This would encourage the sale of drugs at low prices but also imply an effort to simplify the administration to patients, in order to improve their effectiveness. Furthermore pharmaceutical companies would be interested in actively supporting the health services of less developed countries, to facilitate drugs distribution to their citizens.

The proposal hence contemplates a link between innovators reward and therapeutic value of new products, as also suggested by Hollis ([4]) and later by Love and Hubbard ([5]). In particular, Hollis suggests the institution of an international fund (IPIF) aiming to support pharmaceutical innovation out of the current system based on intellectual property rights, although with a voluntary adhesion by the economic operators in the sector. The fund should deliver to the creators of each new drug a money amount corresponding to the net average therapeutic advantage for a predefined number of years. This solution well fits with the institution of an alternative incentive system remunerating the development of new medicines commensurably to therapeutic utility and health benefits, as proposed by Pogge. Indeed Hollis and Pogge share many views about this topic. In a later joint work they describe in detail a possible Health Impact Fund (HIF) for the reward of pharmaceutical innovation under the alternative system ([6]).

Indeed Pogge is aware that his scheme might discourage the development of pharmaceutical products with scarce therapeutic value but anyway appreciated by their consumers. These products could remain subjected to the traditional patent system that makes them remunerative
because of existing demand and possibility of requiring high prices without the ethical problems of essential drugs.

The third element of proposed reform is about the finding and allocation of financial resources to support the scheme, as well as the capability of making the adopted measures acceptable for all the involved actors i.e. governments, pharmaceutical industry and worldwide public opinion. Undoubtedly the rich countries would be the greatest contributors to scheme funding, but according to the author it would not be an exorbitant burden. Pogge has estimated that the probable additional expenditure for the most developed nations could amount to 70 billion USD per year i.e. less than 0.3% of their total GDP. This sum corresponds to an additional yearly cost for each individual in affluent countries not exceeding the 70 USD. Furthermore, less financial resources would probably be required at the beginning. According to Hollis and Pogge, the initial annual commitment for HIF funding could be 6 billion USD only. At this scale it would be possible to support the development of about two new drugs per year. The fund size is scalable, so it may be enlarged if the system works well.

Pogge finds several arguments that could persuade the citizens of high income countries to accept the design, apart the moral unacceptability of current situation. Above all the sale prices of essential medicines would drastically decrease everywhere, facilitating their purchase by poor inhabitants of affluent countries too. This would have redistributive social effects, with a higher equality in the access to medical care in each nation. Rich people would be benefited too, although at a lesser degree.

Another key argument is the possibility of showing to less advantaged peoples the goodwill of the affluent minority of mankind. The acceptance of the project would tangibly testify the sincere efforts of the citizens of wealthy countries to improve the life conditions of the poorest areas of the globe. After all, the luck of being born in an advanced nation should spontaneously induce a moral obligation to at least a little effort to help those who live in worse conditions. This argument could be scarcely effective in a stiffly selfish society, but the strong impulse to innovation under the proposed scheme would certainly have beneficial effects onto the economy and the employment in the countries taking over the research and development activities. New high profile job opportunities would arise in pharmaceutical industry and medical research institutions. Furthermore the treatment of diseases in developing countries would prevent epidemic outbreaks that could easily reach other parts of the world. The recent clamour due to swine flu has shown the
acute awareness of the danger of pandemics. Indeed the so-called Spanish Flu epidemics of 1918, facilitated by movements of masses of individuals at until then unequalled scale because of the First World War, anticipated the possible epidemiologic consequences of contemporary globalization. Finally, the effort required by the project, promoting a better reciprocal understanding, would contribute to avert possible conflicts and social and political instability in developing countries. Considering current international conjuncture this would not be a minor advantage. Apart from ethical motivations, the objective material convenience in reducing the morbility in poor countries would make the proposal of Pogge an interesting option for the less altruist individuals too. Supporters of the author believe this would be enough to soften the possible oppositions to the reform in the affluent nations.

1.3. Potential flaws

The proposal of Pogge undoubtedly represents an original contribution to the discussion about the best way to improve pharmaceutical research by reducing the biases due to current incentive system. Nevertheless the author is aware of the problems related to its practical implementation. Pogge does not provide a detailed description of the allocation of financial resources for the research activities, although he recognizes the complexity of the task. For instance, if two or more drugs can treat an illness, earning corresponding to their therapeutic value should be divided between the respective patent owners, proportionally to the resulting effectiveness in trials and to sales volume. The situation would be even more complicated for therapies requiring the simultaneous administration of more drugs, as commonly occurring for HIV. These drugs are often developed by different producers. The reform proposal should then define with extreme care the modalities of reward in these cases, providing to the innovators enough high earnings to incentivize the research and development activities.

The workability of the scheme may be damaged by the dishonest behaviour of some players. A pharmaceutical firm could declare a sale volume higher than the real one, for receiving undue larger rewards. This could mainly occur for the sales in developing nations, having less efficient and often corruption prone health services. There is also the danger of collusive agreements between the administrators of scheme financial resources and the pharmaceutical corporations. This risk could anyway be mitigated assigning for the rewards a year lump sum, without the possibility of changing its amount. This expedient could lead to reciprocal compensation of
eventual pressures by different pharmaceutical firms. Indeed the fixed reward pool is the proposed baseline for HIF design by Hollis and Pogge, although they do not exclude alternative arrangements.

An interesting critical review of the reform proposal is developed by Sonderholm ([7]). The author analyses the scheme of Pogge, individuating some open issues and flaws. As for the supposed lack of drugs for the treatment of diseases in low income countries, Sonderholm considers the case of HIV therapy in Africa. In several African countries many anti-retroviral drugs are not patented and are therefore available at low prices. Although it is not really clear if all required drugs for an effective therapy are free, at least for HIV anti-retroviral medicines no serious access problem due to intellectual property rights no longer occurs. Sonderholm believes that access to drugs is often more limited by the ineffectiveness of local public health services than by sale price. The lack of material infrastructures and human resources would constitute a barrier to the delivery of essential drugs also if they were made available for free. Indeed Pogge is aware of this problem but in his writings he expresses the belief that the pharmaceutical companies would be interested in contributing to the improvement of health services in developing countries. By facilitating the distribution of new products to as many people as possible they would increase their therapeutic value and therefore the reward. However, Sonderholm has some doubts about this outcome. A pharmaceutical firm could be not so much available to improve medical services of a country if this advantages its competitors too. Furthermore, the ineffectiveness of health systems in low income countries evidences another potential flaw in the proposal. A poorly performing national health service may not be suitable to the delivery of high tech drugs, requiring specialised professionals or too many resources for the administration. Indeed in a Third World country even the availability of potable water may represent a barrier for the large scale delivery of a drug. Less performing but more easily administrable products are a better option in these situations. This would reorient the pharmaceutical research toward less technologically advanced products and may facilitate the emergence of companies that are dedicated to the specific health needs and care capabilities of developing countries. According to the scheme of Pogge the main financial contribution to this system would come from advanced nations. However, a pharmaceutical research aiming to low tech production would not create high profile jobs in the sector in the affluent countries. According to Sonderholm this situation would probably benefit the low income countries but not encourage the inhabitants of developed nations to support the scheme. In the end, the financial burden of funding the plan of Pogge would fall upon the shoulders of affluent
countries without meaningful concrete advantages for their citizens. Rather than decreasing the price of commonly marketed drugs in their countries, these consumers should finance with their taxes the development of medicines to be used in other world areas, while research of more suitable products to their domestic social, economic and technological context would be neglected.

To be honest, Sonderholm perhaps excessively neglects some positive fallouts of the proposal, like the better reciprocal understanding of developing and rich countries and the lessening of social and political conflicts, both at national and international level. However, some of his concerns are justified. For instance, the problem of promoting pharmaceutical research for rare diseases remains an open issue for Pogge too. If the potentially sellable quantity of a drug amounts to relatively few units, reward to developers under the scheme of Pogge will be low with respect to the research costs. Indeed the proposed alternative incentive system seems mainly suitable to deal with large scale diffused pathologies rather than with orphan diseases. In the same way, although for different reasons, the proposal of Pogge cannot work for basic pharmaceutical research. Grant funding remains more adequate to support innovation not providing a direct health benefit.
2. Alternative incentive system reward

2.1. The burden of diseases

Fundamental premise for the assessment of the proposal of Pogge is the individuation of a parameter satisfactorily expressing the therapeutic benefits of the medicines. It is not possible to have neither a true measurement of these benefits nor a parameter unambiguously aggregating them. Sale prices only imperfectly express the therapeutic value of a drug or vaccine. Furthermore, medicine purchase is not usually decided by the patient as for other ordinary goods or services, but following a medical prescription i.e. according to the judgment of another person with a better understanding of the matter. Purchase expenditure itself does not usually lie on the patients only. Contributions may come from public health services, no-profit organization or health insurance companies, depending on the country. All these aspects make sale prices a relatively inadequate index of medicine true value, differently from other products and services.

A parameter that better represents the therapeutic value of pharmaceutical treatments is Quality-Adjusted Life Year, or QALY. It expresses the benefit from medical intervention to reduce disease damages, with reference to both the quality and duration of life. It 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. Weighting coefficient is 1 for each year in perfect health, while lower values are used for the years of illness or infirmity, down to 0 in case of death. Indeed the use of QALY is not universally accepted by the scientists. Defining a condition of perfect health is not easy and some authors think that, for very severe infirmities, life conditions may be worse than death itself, so a negative value for weighting coefficient is plausible. Anyway, although with these limitations, QALY is a more objective indicator of the value of a medicine than monetary price. In the end, the international organisations and agencies financing general pharmaceutical expenditure in the poor areas of the globe or the care of specific illnesses often check the effectiveness of adopted measures with analogous parameters, like the reduction of incidence of pathologies or the decrease of mortality caused by them.

It is to be noted that QALY is not the unique parameter that may be used to express health benefits. An alternative measurement unit is represented by Disability-Adjusted Life Year, or DALY. The concept was first introduced in the World Development Report of 1993, issued by
World Bank with the WHO support ([8]). 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 for incident cases of the health condition. In their work of 2008 Hollis and Pogge acknowledge that DALY and QALY concepts are similar, although they retain specifically distinct features ([6]). For the authors, QALY would be more representative because it is defined through population-level assessments rather than by groups of public health experts. Indeed there have been many discussions about which parameter may better characterise health conditions. For the aim of the present study DALY health measurements are of interest because they are usually adopted by international health organisations, above all the WHO. In a WHO report about global burden of disease (GDB) projections of DALYs corresponding to several death causes were presented ([9]). In Table 2.1-1 the 2008 values in DALYs of global burden of communicable diseases from the aforementioned document are reported. They provide a quantitative insight into the worldwide impact of the most severe transmissible illnesses that should be the main target of pharmaceutical research efforts in the frame of the alternative reward system. It is interesting to note that, taking into account the infectious diseases group only, HIV and malaria count for about one third of total DALYs. Although the category of diarrhoeal diseases has a larger burden than HIV, it includes several illnesses having diarrhoea as main symptom, like cholera, typhoid fever and bacillary dysentery. Worldwide weight of painful tropical diseases is much less relevant. As for the respiratory infections group, those affecting lower respiratory tract contribute for quite the totality of disease burden of the category. They mainly consist of bronchitis and pneumonia. As shown in Table 2.1-1, considering both the groups, lower respiratory tract diseases would outweigh even HIV. Indeed several effective drugs are available to deal with respiratory infections, differently from HIV and malaria, nowadays still representing a challenge for medical research. However, even if medicines are already in place, their effectiveness may decrease over time, because of the increasing resistance of bacterial or viral strains. In some cases a vaccine does not protect against all the disease subtypes, as in the case of tuberculosis. Indeed the discovery of vaccines for HIV/AIDS, malaria, tuberculosis and Dengue fever has been mentioned by several authors like the research target in the next years1.

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1 For instance, see the presentation by S. Lee ([10]).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Thousands DALY</th>
<th>Percent</th>
<th>Partial</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>34,217</td>
<td>11.32%</td>
<td>8.56%</td>
<td></td>
</tr>
<tr>
<td><strong>STDs excluding HIV</strong></td>
<td>10,425</td>
<td>3.45%</td>
<td>2.61%</td>
<td></td>
</tr>
<tr>
<td><strong>HIV/AIDS</strong></td>
<td>58,513</td>
<td>19.37%</td>
<td>14.63%</td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhoeal diseases</strong></td>
<td>72,777</td>
<td>24.09%</td>
<td>18.20%</td>
<td></td>
</tr>
<tr>
<td><strong>Infantile diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pertussis</em></td>
<td>9,882</td>
<td>3.27%</td>
<td>2.47%</td>
<td></td>
</tr>
<tr>
<td><em>Poliomyelitis</em></td>
<td>34</td>
<td>0.01%</td>
<td>0.01%</td>
<td></td>
</tr>
<tr>
<td><em>Diphtheria</em></td>
<td>174</td>
<td>0.06%</td>
<td>0.04%</td>
<td></td>
</tr>
<tr>
<td><em>Measles</em></td>
<td>14,853</td>
<td>4.92%</td>
<td>3.71%</td>
<td></td>
</tr>
<tr>
<td><em>Tetanus</em></td>
<td>5,283</td>
<td>1.75%</td>
<td>1.32%</td>
<td></td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td>11,426</td>
<td>3.78%</td>
<td>2.86%</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis B</strong></td>
<td>2,068</td>
<td>0.68%</td>
<td>0.52%</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis C</strong></td>
<td>955</td>
<td>0.32%</td>
<td>0.24%</td>
<td></td>
</tr>
<tr>
<td><strong>Malaria</strong></td>
<td>33,976</td>
<td>11.24%</td>
<td>8.50%</td>
<td></td>
</tr>
<tr>
<td><strong>Tropical diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Trypanosomiasis</em></td>
<td>1,673</td>
<td>0.55%</td>
<td>0.42%</td>
<td></td>
</tr>
<tr>
<td><em>Chagas disease</em></td>
<td>430</td>
<td>0.14%</td>
<td>0.11%</td>
<td></td>
</tr>
<tr>
<td><em>Schistosomiasis</em></td>
<td>1,707</td>
<td>0.57%</td>
<td>0.43%</td>
<td></td>
</tr>
<tr>
<td><em>Leishmaniasis</em></td>
<td>1,974</td>
<td>0.65%</td>
<td>0.49%</td>
<td></td>
</tr>
<tr>
<td><em>Lymphatic filariasis</em></td>
<td>5,941</td>
<td>1.97%</td>
<td>1.49%</td>
<td></td>
</tr>
<tr>
<td><em>Onchocerciasis</em></td>
<td>389</td>
<td>0.13%</td>
<td>0.10%</td>
<td></td>
</tr>
<tr>
<td><strong>Leprosy</strong></td>
<td>194</td>
<td>0.06%</td>
<td>0.05%</td>
<td></td>
</tr>
<tr>
<td><strong>Dengue</strong></td>
<td>670</td>
<td>0.22%</td>
<td>0.17%</td>
<td></td>
</tr>
<tr>
<td><strong>Japanese encephalitis</strong></td>
<td>681</td>
<td>0.23%</td>
<td>0.17%</td>
<td></td>
</tr>
<tr>
<td><strong>Trachoma</strong></td>
<td>1,334</td>
<td>0.44%</td>
<td>0.33%</td>
<td></td>
</tr>
<tr>
<td><strong>Intestinal nematode infections</strong></td>
<td>4,013</td>
<td>1.33%</td>
<td>1.00%</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>28,558</td>
<td>9.45%</td>
<td>7.14%</td>
<td></td>
</tr>
<tr>
<td><strong>Total infectious and parasitic diseases</strong></td>
<td>302,144</td>
<td>100.00%</td>
<td>75.55%</td>
<td></td>
</tr>
<tr>
<td><strong>Lower respiratory infections</strong></td>
<td>94,511</td>
<td>96.65%</td>
<td>23.63%</td>
<td></td>
</tr>
<tr>
<td><strong>Upper respiratory infections</strong></td>
<td>1,787</td>
<td>1.83%</td>
<td>0.45%</td>
<td></td>
</tr>
<tr>
<td><strong>Otitis media</strong></td>
<td>1,488</td>
<td>1.52%</td>
<td>0.37%</td>
<td></td>
</tr>
<tr>
<td><strong>Total respiratory infections</strong></td>
<td>97,786</td>
<td>100.00%</td>
<td>24.45%</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>399,930</td>
<td></td>
<td></td>
<td>100.00%</td>
</tr>
</tbody>
</table>

Table 2.1-1: Global burden of communicable and infectious diseases - 2008 estimates ([9])
2.2. The quantification of incentives

In the work of Hollis and Pogge reward system main features are presented, although the authors admit that many elements are still to be addressed ([6]). In the end, the alternate incentive system will work only if pharmaceutical business operators find it advantageous. Therefore the workability of the proposed solution shall be examined taking in account the perspective of developers.

With the health fund system the reward for a new medicine will be proportional to the total provided benefits. An approximative quantification is proposed in Hollis and Pogge study. Therapeutic improvement per patient is defined as the difference between the average impacts of the new medicine and pre-existent baseline treatment, expressed in QALYs or DALYs. Overall benefit is the product between total number of patients and average individual health improvement. Although the authors themselves acknowledge that this is a crude aggregation, it evidences an important aspect of the reward system. Delivered earnings from two equally effective drugs for different illnesses will be proportional to their respective disease burdens. This situation would incentive the research of new medicines for much diffused illnesses, but it would not encourage the development of effective remedies for circumscribed diseases. For instance, a 20% successful vaccine against HIV would outweigh a 100% effective vaccine against Chagas disease. Although this intrinsic limitation of the proposal of Pogge has been already acknowledged for orphan diseases, it is remarkable that it may also occur for not so rare pathologies.

From previous considerations an analytical characterisation of innovation reward with the HIF scheme described by Hollis and Pogge can be derived. Annual reward to the developer will be equal to the product of available amount of funds and the share of worldwide health improvement due to the discovered medicine. It is to be noted that, assuming that funding is constant as in Hollis and Pogge baseline scheme, the annual reward may change in a not deterministic way over the compensation period. This may happen also if medicine delivered health benefits remain the same and no new, better remedy for that disease is discovered. The development of effective products to cure other pathologies may reduce the weight of global health improvement contribution due to that medicine, so lowering the amount of reward to its developer. To characterise this situation, share of health global improvement due to the medicine for the pathology of interest may be expressed as:
\[ h_d = \frac{H_d}{H_d + \sum_{i=1, i \neq d}^{N} H_i} \]

where:

- \( H_d \) is the health improvement due to the medicine for the \( d \)th disease i.e. the pathology of interest, expressed in a given measurement unit like QALY or DALY.
- \( H_i \) is the health improvement due to other HIF rewarded products.
- \( N \) is the total number of HIF rewarded products.

Previous considerations show that definition of health improvement contributions is not trivial. A possible solution is to express each contribution as the product of a medicine effectiveness coefficient and a disease burden parameter. The former term corresponds to the quality or efficacy of discovered product and can be given as a percent value\(^2\). The definition of the latter term is trickier. Distribution of drugs and vaccines usually requires years to achieve the global coverage of target population. This especially occurs for the remedies to diseases in less wealthy countries, often lacking of adequate logistic and medical infrastructures. Time profile of global coverage level can be derived from past experiences in worldwide immunization campaigns. As explained in the Appendix A.1, the progression of diphtheria, tetanus and pertussis (DTP3) immunization coverage over time is a useful reference. Coverage time profile function can be derived by interpolating the historical DTP3 immunization data. It is to be noted that resulting profile represents the share of annual target population that is vaccinated for the first time each year, not the total number of immunized individuals at a given time after campaign beginning.

\(^2\) It is to be remembered that, at least in medical context, efficacy and effectiveness are not the same thing. The former is mostly referred to the patient healing capability of a medicine in controlled conditions, for instance a medical trial context. The latter indicates the health benefits of the product in population at large. To assess the therapeutic benefits at worldwide level the parameter of interest is effectiveness rather than efficacy, that is more strictly associated to the quality of a medicine.
Drugs and vaccines need different approaches in the evaluation of therapeutic benefits. A drug is administered only to already sick individuals, while aim of vaccination campaigns is disease prevention. Furthermore, some drugs succeed in definitively eradicating a disease within a limited period; others can improve the life quality of the patients but need a lifelong administration, like the HIV/AIDS anti-retroviral medicines. This will imply differences in resulting therapeutic improvement definitions.

From the previous considerations the reward share of Eq. 1 for a generic year may be rewritten as follows:

\[
2 \quad h_{d,y} = \frac{Q_d \cdot G_d(y)}{Q_d \cdot G_d(y) + \sum_{i=1,i\neq d}^{N} Q_i \cdot G_i(y)}
\]

\(Q_d\) and \(Q_i\) are the qualities of health fund rewarded medicines, intended as their efficacy in curing the corresponding pathologies, while \(G_d(y)\) and \(G_i(y)\) are the temporal profiles of the disease burdens that should be reduced or prevented by the new products distribution. A simplification is possible assuming that all the fund rewarded medicines share the same global distribution time pattern, so that \(G_d(y)\) and \(G_i(y)\) are identical. This allows reducing the expression of Eq. 2 to:

\[
3 \quad h_d = \frac{Q_d \cdot G_{d0}}{Q_d \cdot G_{d0} + \sum_{i=1,i\neq d}^{N} Q_i \cdot G_{i0}}
\]

\(G_{d0}\) and \(G_{i0}\) represent the annual reference values of disease burdens and are differently defined for drugs and vaccines. Indeed this is not a general situation. Medicines may have different coverage temporal profiles, depending on their introduction time and specific characteristics. For instance, temporal profiles may be different for drugs and vaccines.

From the point of view of the developer of the medicine for the pathology of interest, the efficacy of other products represents an exogenous random variable, with values comprised between 0 and
1. Therefore it is eager to characterise the quality of these products by using a Beta probability density function. By definition, the expected value of a function of random variables is:

\[ E[h_d] = \int_0^1 \int_0^1 \frac{Q_d \cdot G_{d0}}{Q_d \cdot G_{d0} + \sum_{i=1,i \neq d}^N Q_i \cdot G_{i0}} \cdot f_Q(Q_1, \ldots, Q_{i \neq d}, \ldots, Q_N) \cdot dh_1 \cdot dh_{i \neq d} \cdot dh_N \]

The lower and upper bound of integration intervals are respectively set to 0 and 1, according to definition range of Beta density functions. The function \( f_Q \) represents here the joint density of the \( Q_i \) variables. It is reasonable to assume that they are statistically independent, provided that corresponding research and development activities are uncorrelated. Therefore their joint density will be equal to the product of respective density functions that, as previously written, are Beta distributions. Eq. 4 hence becomes:

\[ E[h_d] = \int_0^1 \int_0^1 \frac{Q_d \cdot G_{d0}}{Q_d \cdot G_{d0} + \sum_{i=1,i \neq d}^N Q_i \cdot G_{i0}} \cdot \prod_{i=1}^N f_{Q_i}(Q_i) \cdot dh_i \]

The quality \( Q_d \) of the product of interest only depends on the research and development activities performed by the innovator. Therefore \( Q_d \) can be taken as a constant term in the integrals in Eq. 5.

From previous results it is possible to express the expected net present value (NPV) at the beginning of reward period. If the medicine is sold at a price equal to the production marginal cost the expected NPV would only consist of the health fund reward contributions, so that:

\[ V_d = S_0 \cdot \sum_{y=1}^{N_g} \frac{1}{(1+r)^y} \cdot E[h_{d,y}] \]

---

3 The reference for the characterisation of statistical issues is the work of Papoulis et al. ([11]); in particular, for Beta density function, see page 91.

4 See par. 6.4 of [11].
With the simplifying assumptions leading to Eq. 3 it is:

\[
V_d = S_0 \cdot E[h_d] \cdot \sum_{y=1}^{N_R} \frac{1}{(1+r)^y} = S_0 \cdot E[h_d] \cdot \frac{1}{r} \left[ 1 - \frac{1}{(1+r)^{N_R}} \right]
\]

In the expressions \( S_0 \) is the annual fixed sum of health fund, \( N_R \) is the number of reward years and \( r \) is the annual discount rate. Use of discrete actualisation formula is here appropriate because the health fund payments do not consist of a continuous cash flow but are delivered at the end of each year, proportionally to the evaluations of annual therapeutic benefits of the medicine.

### 2.3. Uncompensated costs

Hollis and Pogge proposal does not contemplate a free-of-charge distribution of the new product. It is supposed that the producer will demand a price equal to production and distribution marginal costs that are indeed rather low. In a research about anti-retroviral drugs Lucchini et al. show that price per unit has decreased to less than 1 USD from 1997 to 2002, partly thanks to the diffusion of generic products ([12]). It is to be noted that these figures only correspond to the cost of a single unit of the medicine. In case of anti-retroviral drugs each patient shall regularly assume a combination of more medicines that strengthens the immune defence system and slows down the virus diffusion. Overall annual marginal cost per patient of triple drugs in highly active antiretroviral combination therapies (HAART) may amount to about 200 USD. Although it probably remains an unaffordable expenditure for a large number of HIV patients in low income countries, medicines purchase could be done by governmental health services and non-profit organizations. Therefore uncompensated costs due to manufacturing and distribution expenditures are expected to be quite negligible. Nevertheless, the developer is interested in compelling the distribution of the new product to as many people as possible, to maximize the health benefits and hence its reward. This could lead to sell the medicines at a lower price than the aforementioned marginal costs, or promote their distribution in different ways. For instance, the developer could support the local health services in low income countries, by financing their equipment improvement or personnel training. This kind of efforts would help to solve the so-called last mile problem that Hollis and Pogge recognize to be critical for the achievement of actual
therapeutic improvement from new medicines. However, they would also represent additional costs that could not be compensated by sale price, although they are expected not to match the current high promotional and advertising expenditures of pharmaceutical corporations under the traditional patent system.

Presence of uncompensated costs proportional to production requires a more complex expression for NPV than Eq. 7. Annual medicine quantity that is produced and delivered over time is to be evaluated. It is given by the product of the global coverage time profile function and the annual target population of the medicine. Differently from rewards, cash flows corresponding to costs continuously take place during the year. Therefore expected NPV is properly defined as follows:

\[
V_d = S_0 \cdot E[h_d] \cdot \sum_{y=1}^{N_d} \frac{1}{(1+r)^y} - c_u \cdot q_d \cdot \int_0^{T_R} D_d(t) \cdot e^{-r_c t} \cdot dt
\]

In the formula \( c_u \) is the uncompensated annual cost per patient and \( q_d \) is the annual target population. Both are supposed to remain constant over time. The function \( D_d \) corresponds to the share of annual target population receiving the medicine according to a specific time pattern.

Time quantities are expressed in years, so that the numerical value of reward period \( T_R \) corresponds to \( N_R \). Instead of \( r \) in the integral the continuous discounting rate \( r_c \) is used:

\[
r_c = \ln(1 + r)
\]

This allows rewriting the expression as:

\[
V_d = S_0 \cdot E[h_d] \cdot \sum_{y=1}^{N_d} e^{-r_c y} - c_u \cdot q_d \cdot \int_0^{T_R} D_d(t) \cdot e^{-r_c t} \cdot dt
\]

As for health improvement, quantification of eventual uncompensated costs under the Pogge’s reward system is not trivial. Evaluations of cost effectiveness of interventions for diseases like
HIV/AIDS, malaria and tuberculosis for world regional areas are reported in WHO CHOICE program studies ([13]). Unfortunately, average annual costs per capita of hygienic measures and pharmacological therapies are derived with reference to the overall population of each area rather than to the disease affected people only. Therefore it is difficult to derive realistic and representative estimates for aforedescribed uncompensated costs. For this reason, in the numerical evaluations reported in the present document it is assumed that all costs related to medicine production and distribution are covered by sale price.

2.4. Research duration and rewarding period

In the preliminary design of health fund the reward duration is assumed equal to ten years. A shorter period of five years is proposed when new therapeutic uses of existing drugs are registered under the scheme ([6]). Although the traditional patent has a nominal duration of at least twenty years, it is to be remembered that its effective marketing life is shorter, assuming that patent registration is done in the first stages of research and development activity. Several years are usually necessary before a new product is developed, tested, authorised by competent health authorities and made available to the market.

Average duration of research and development phases has been evaluated by the principal world pharmaceutical industry organisations i.e. EFPIA in the European Union and PHRMA in the United States. As explained in their 2009 figures reports, it may require from ten to fifteen years after the beginning of research before a newly discovered drug is marketed ([1], [14]). In the process two main phases are identified. The former corresponds to the initial development of a new drug or vaccine for a given disease. In the search of a possible treatment the scientists assess the potential therapeutic properties of existing chemical compounds and natural molecules or develop new chemical entities (NCE). After having demonstrated the therapeutic action of the compound with preliminary experiments, preclinical tests are required, in laboratory conditions and sometimes on animals. Although a drug is effective to treat a disease, it may severely harm the human organism because of possible secondary effects. Maybe a compound is too dangerous to be given to patients, also if it proves successful against the disease. Preclinical tests may lead to improvements and modifications of candidate medicine. They are usually mandatory before direct

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5 Under current intellectual property laws a supplementary protection certificate (SPC) of further five years may be required to prolong the exclusivity of the patentee.
tests on human beings are authorised by competent institutions. The overall duration of this first phase is usually comprised between three and six years.

The latter phase mainly consists of clinical tests, usually contemplating three sub phases. In the first sub phase the safety for human beings is verified and possible secondary effects are investigated, generally with tests on small groups of healthy volunteers. The second sub phase foresees tests on small groups of actual patients, to verify the effectiveness of the product in the treatment of the disease. Finally, in the third sub phase larger scale tests on patients are performed. They are useful to find possible secondary effects that may be harmful but are not easy to be detected because of their statistical rarity. Overall duration of the whole clinical testing phase is usually about seven years.

After having successfully passed the clinical tests, the application for marketing and distribution can be presented to national health authorities. After their approval, the new drug can be commercialised. The developer will scale up its facilities, by building new infrastructures if required, to produce the drug in large quantities, in order to meet the market demand. Indeed scaling up of production facilities is often done before approval is formally released, if no surprises are expected. A graphic representation of research and development time sequence is shown in Figure 2.4-1.

In the frame of Pogge proposal, as described in his joint work with Hollis, the health fund should pay the reward to the developer of a new drug after the market approval and according to its therapeutic effectiveness ([6]). Therefore the payoff period would start after registration of the medicine under the fund scheme. The proposal foresees ten years for a new medicine. Payoff amount would uniquely depend on yearly evaluations of 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 after the market approval. Therefore the innovator would then have only a few years to sell the medicine in monopolistic conditions. The alternative scheme does not present these problems. The innovator has the certainty to be paid for the predefined period. Indeed, as previously noted, this will address research efforts towards really breakthrough medicines. However, firms will choice to adhere to the alternative reward scheme only if it proves more convenient than the traditional system.
In Figure 2.4-2 the timing of patent application has been indicated quite at the beginning of research process. Indeed this point needs some deepening. In most countries patent laws contain a utility requirement. A patent will be delivered for a new product only if it has somewhat a real utility. In the United States the Patent Act of 1952 explicitly requires that patents are released only for “useful” inventions. This requirement may generate some problem for pharmaceutical patent applications. Scientists and pharmaceutical corporations are obviously compelled to obtain patent protection on compounds of interest as soon as possible, although therapeutic properties and secondary effects have not been yet fully investigated. Nevertheless, if application is filed too early, it may be troublesome to demonstrate that the new compound is “useful” in the sense that it may lead to the development of a marketable and not hazardous medicine. Interpretation of the utility requirement may change depending on country legal systems and court pronunciations. However, in the United States and European Union, patent law enforcement is not too rigid for pharmaceutical research. Although many applications contain some experimental evidence for the properties of products under study, this is not required in principle. Furthermore, only preliminary tests are usually reported in the applications, generally performed in not representative laboratory conditions or over animals. Patent registration does not exclude that later clinical tests lead to discard the candidate drug as suitable for practical use.

Indeed only a few patented compounds for pharmaceutical use really reach the market approval phase. Although an early patenting may sometimes seem premature, it has the advantage of avoiding research duplications by pharmaceutical firms, so it may be considered beneficial. However, because of the aforementioned average research and development duration, early patent application may reduce only to a few years the real earning period.
Figure 2.4-1: Time sequence and logical phases of research and development process

Figure 2.4-2: Reward timeline concept with usual patent exclusivity and alternative system
2.5. Pharmaceutical research average costs

Some assumptions may be done about the amount of required investments for discovery and preclinical research, for clinical trials and for production infrastructure building. Indications are found in existing literature and industrial statistics. About this issue there has been a lot of debate. A WHO review of the main worldwide health issues reported an average cost of 800 million USD for developing a new drug ([15]). The figure comes from a study by DiMasi, Hansen and Grabowski ([16]). In a later work DiMasi and Grabowski found even higher costs for drugs developed by biotechnological firms, up to 1.2 billion USD ([17]). Nevertheless 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 costs are calculated taking in account the transition probability of each subphase, as defined in Figure 2.4-1. This delivers an average out-of-pocket cost of Phase 2 amounting to about 60 millions USD. For Phase 1 a similar outlay 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 in account the success rate. This indeed inflates the final results, up to the previously mentioned amounts.

Severe criticism about this approach has been issued from many parties. Specifically, in their evaluations DiMasi and his colleagues would have 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 expenditure of pharmaceutical firms to discover and develop new medicines. Furthermore, the reference data sample would be biased towards the producers of blockbuster drugs, so it would not be representative of the development process of medicines for diseases primarily affecting the developing countries. Another objection is that the authors would not have considered the relevant tax deductions that are 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 ([18]). This would be the...

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* The sum is expressed in 2000 USD.

* The original figure was 65.5 millions in 1990 USD. Public Citizen has inflated it to year 2000.
actual expenditure for a pharmaceutical firm to develop a NCE, including failures. The figure is compliant to a 2001 evaluation of clinical trials cost by the Congress, reporting 75 million USD.

Other useful data are available for specific research issues. In their work about investments in AIDS vaccine development, Batson and Ainsworth indicate for basic and preclinical research a required investment of 20 million USD, while the clinical testing phase would need 40 million USD ([19]). Further 100 million USD are said to be necessary for scaling up the manufacturing capacity, for large scale production of the new medicine to cope with developing countries demand. Indeed these data are only partially representative, being referred to the research and development of a vaccine for a specific disease. Drugs and biopharmaceuticals may present different characteristics and development issues.

Higher costs than those mentioned in Batson and Ainsworth work can be found for manufacturing plants building too. For instance, in 2009 Sanofi-Aventis company has started the construction of a new vaccine manufacturing facility in France, to become operative within 2013, with an investment of 350 million € i.e. about 460 million USD. The facility should produce up to 100 million doses of a new vaccine for Dengue fever. Nevertheless an existing pharmaceutical producer will exploit its available infrastructures as far as possible. Therefore it is reasonable to assume that required investment for large scale production of a new medicine is comprised between 50 and 500 million USD.
3 The model

3.1. Research as a process with stochastic parameters

The goal of the present work is to assess economic sustainability of a pharmaceutical research project under the incentives proposed by Pogge. This needs developing an analytical model considering the specific issues of innovation process. The model shall allow estimating the expected NPV of the project, actualised at the beginning of research. The innovator will start the activities to find a remedy to a specific pathology only if expected NPV is positive. Otherwise there will be no convenience to start the activity. In theory Pogge’s alternative incentives should make convenient the development of essential drugs and vaccines that are not enough remunerative under the conventional patent system.

Model definition would not be too demanding if all the research describing parameters were deterministic and known. Unfortunately, this is not a realistic assumption. An important issue is the length of the two research phases, as defined in the previous paragraph. Although typical duration values can be found in literature, giving a preliminary reference, they do not represent the actual length of Phase 1 and Phase 2. Occurrence of unpredictable events may positively or negatively affect the research performance and outcomes. Phases may result shorter or longer than their average duration, defined for comparable research activities. The main criticality of such random variability for the developer is that it affects costs. In a very simple model it is comfortable to assume that investments occur at the beginning of each phase and have known and fixed amounts. However, in real conditions, investments will be continuous over time, in both the phases. Only investments to build or upgrade industrial plants for large scale production, after the new medicine has been successfully developed, can be realistically supposed deterministic. Assuming that investment time rate is constant and known, total invested money will depend on phase length and therefore it will be a random variable too. Another relevant issue is the quality of research outcome, or the efficacy of final product. Minimum acceptable quality of a drug or a vaccine may be defined in advance, but actual efficacy is not a priori known.

The proposed approach to deal with the aforementioned issues is based on Hsu and Schwartz work about the economic feasibility of a HIV/AIDS vaccine ([20]). 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 Phase 1 and Phase 2 durations and costs can be characterised by modelling the latter as stochastic processes. Indeed, 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 intended as 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$^8$.

In Phase 1 they are described by the following relations:

$$dK_1(t) = -I_1 \cdot dt + \sigma_1 \cdot dW_1(t) \quad 0 \leq t < \tau_1$$
$$dK_2(t) = \sigma_2 \cdot dW_2(t) \quad 0 \leq t < \tau_1$$

In Phase 2 only $K_2(t)$ will be not null. Describing equation is:

$$dK_2(t) = -I_2 \cdot dt + \sigma_2 \cdot dW_2(t) \quad \tau_1 \leq t < \tau$$

The terms in the equations have the following meaning:

- $\tau_1$ is the actual completion time of Phase 1.
- $\tau_2$ is the actual completion time of Phase 2.
- $\tau$ is the actual length of the research, given by the sum of $\tau_1$ and $\tau_2$.
- $I_1$ is Phase 1 nominal investment rate, in money per time units.
- $I_2$ is Phase 2 nominal investment rate, in money per time units.
- $\sigma_1$ is the $K_1(t)$ process standard deviation, or volatility of Phase 1 investment.
- $\sigma_2$ is the $K_2(t)$ process standard deviation, or volatility of Phase 2 investment.
- $dW_1$ is the $K_1(t)$ process Brownian motion term.
- $dW_2$ is the $K_2(t)$ process Brownian motion term.

$^8$ An exhaustive illustration of Wiener or Brownian stochastic processes and related theoretical issues is presented in [21]. Modelling of investment under uncertainty is extensively treated in [22].
Time sequence of research phases is represented in Figure 3.1-1. Having set to 0 the research beginning, its total length $\tau$ will correspond to completion time instant.

Basically, at the beginning of the research there is an expectation about Phase 1 and Phase 2 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:

14 \[ K_1(0) = I_1 \cdot \tau_1(0) \]
15 \[ K_2(0) = I_2 \cdot \tau_2(0) \]

In a fully deterministic context $K_1(t)$ and $K_2(t)$ expressions would be directly obtained by integrating Eq. 11 and 13 over time:

16 \[ K_1(t) = -I_1 \cdot t + K_1(0) \quad 0 \leq t < \tau_1 \]
17 \[ K_2(t) = -I_2 \cdot (t - \tau_1) + K_2(0) \quad \tau_1 \leq t < \tau \]

It is interesting to observe that stochastic variability of Phase 1 duration does not only affect its own completion cost but also the expected cost of Phase 2. This reflects the actual features of pharmaceutical research. Delays in preclinical tests affect the expectations about the necessary resources to implement the clinical trials. However, this also means that Eq. 15 may well represent Phase 2 expected cost at the beginning of the research, but it is not anymore valid thereafter, hence the relation of Eq. 12 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 efforts that will be required in the next phase.

To evaluate research project expected NPV at the beginning of the research, the expected completion costs at the time instants corresponding to 0, $\tau_1$ and $\tau$ are to be derived. It has been shown that $K_1(0)$ and $K_2(0)$ are known and deterministic parameters. As for $K_1(\tau_1)$ and $K_2(\tau)$, they are null by definition, because the end of each phase is just defined when no further financial effort
is required. Therefore the only parameter to find is the expected Phase 2 cost at its beginning, or at the end of Phase 1, that is $K_2(\tau_1)$. It is a random variable, whose values can be simulated by using the statistical characterisation illustrated in the Appendix A.2 and derived from the probability density functions of phase lengths.

Analogous considerations can be formulated about the quality or efficacy of research project. As for the other medicines that are rewarded by proposed health fund, the quality of 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 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 instant when research is still in progress, remembering that actual quality of the product will be observable only at the end. The following notation is adopted:

$$Q(t) = E_t[Q(\tau)]$$

Expected quality of 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 earlier quality expectation and phase completion delay referred to its previously expected duration. As for the remaining completion costs, evaluation of expected quality is needed only at $0$, $\tau_1$ and $\tau$ time instants. Its values can be simulated by using the probability density, whose detailed description is reported in the Appendix A.3.

In conclusion, under the previously presented assumptions, 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 Phase 1.
- $\tau_1$, $K_2(\tau_1)$ and $Q(\tau_1)$ at the end of Phase 1, or beginning of Phase 2.
- $\tau$ and $Q(\tau)$ at the end of Phase 2, or at research completion.
It is important to note that the unknown terms are only \( \tau \), \( K_1(\tau) \), \( Q(\tau) \) and \( \tau_1 \) while \( K_1(0) \), \( K_2(0) \) and \( Q(0) \) can be derived or taken from available literature data. As previously observed, a possible set of values for the former group parameters can be obtained by simulation from the corresponding probability density functions, in the Appendices A.2 and A.3. Specifically, the logical steps are the following:

- A \( \tau_1 \) value is drawn by simulation with its density function.
- Result is then substituted in \( K_2(\tau_1) \) density function and a \( K_2(\tau_1) \) value is drawn.
- \( \tau_1 \) and \( K_2(\tau_1) \) values are substituted in \( \tau_2 \) density function and a \( \tau_2 \) value is drawn.
- Expected values for \( \tau_1 \) at \( t = 0 \) and for \( \tau_2 \) at \( t = \tau_1 \) 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 in the mean and variance expressions the previously found values.
- \( Q(\tau) \) is simulated from the corresponding density function, having substituted in the mean and variance expressions the previously found values, \( Q(\tau_1) \) included.

Previous logical sequence is shown in Figure 3.1-2. It is to be noted that it would only give a possible set of state variables values. However, this is the proceeding that will be used in the estimation of expected NPV of the project at the beginning of the research.
Figure 3.1-1: Research and development performance and investments timeline

Figure 3.1-2: Logical sequence of parameters simulation from probability density functions
### 3.2. Determination of economic sustainability

Expected NPV at the beginning of research is calculated in a backward evaluation, performed in three steps corresponding to 0, \( \tau_1 \) and \( \tau \) time nodes. Expected NPV at \( \tau \) is:

\[
\nu(\tau) = e^{-r_c \cdot \tau_3} \cdot \frac{1}{r} \cdot S_0 \cdot E[\theta_d] \cdot \left[ 1 - \frac{1}{(1 + r)^{N_{r}}} \right] - \frac{I_3}{r_c} \cdot (1 - e^{-r_c \cdot \tau_3})
\]

\( I_3 \) is the investment rate for the upgrade of industrial plants for medicine large scale production. The other terms of the expression have been defined in par. 2.2. It is to be noted that the only non-deterministic element is the reward share for the medicine of interest. All the other parameters are assumed to be known. From the result of Eq. 19 it is possible to define the policy function of the innovator at the end of Phase 2. It expresses the convenience or less of the further effort to pass to large scale production and distribution of the new product. In Hsu and Schwartz work it is simply assumed that the innovative firm will go on with plants scaling up if expected NPV at \( \tau \) is positive, otherwise it will cease any related activity. This option to abandon leads to define project present value at \( \tau \) as:

\[
V(\tau) = \Omega[\nu(\tau)] \cdot \nu(\tau)
\]

Here \( \Omega \) is a Heaviside-like step function, representing the abandonment policy of the innovator:

\[
\Omega(x) = \begin{cases} 
1 & x > 0 \\
0 & x \leq 0 
\end{cases}
\]

Evaluation of expected NPV at \( \tau_1 \) 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, expected NPV will correspond to its conditional expectation given the state variables at the end of Phase 1, namely \( K_2(\tau_1) \) and \( Q(\tau_1) \). It will be:
The innovator policy function for the option to abandon or continue the project at \( \tau_1 \) is defined in the same way as at former step. If the conditional expected NPV is positive the innovator will continue to Phase 2, otherwise the project will be abandoned. Therefore resulting present value at \( \tau_1 \) can be expressed as follows:

\[
v(\tau_1) = \mathbb{E}\left[ V(\tau_1) \cdot e^{-r_1 \tau_1} - \int_{0}^{\tau_2} I_2 \cdot e^{-r_2 \tau_2} \cdot dt \bigg| Q(\tau_1), K_2(\tau_1) \right]
\]

Finally, the expected NPV at the very beginning of the research is to be derived. As for its evaluation at the end of Phase 1, it will consist of a conditional expectation given the state variables at 0 time instant, namely \( K_1(0) \), \( K_2(0) \) and \( Q(0) \). Therefore:

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

The innovator will decide to start the 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:

\[
v(0) = \mathbb{E}\left[ V(\tau_1) \cdot e^{-r_1 \tau_1} - \int_{0}^{\tau_1} I_1 \cdot e^{-r_1 \tau_1} \cdot dt \bigg| Q(0), K_1(0), K_2(0) \right]
\]

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

For completeness, it is possible to take in account eventual unpredictable events that are not directly related to the research process but that could negatively affect it. For instance, the project could be damaged if some key persons leave it before the successful conclusion. Another negative event could be 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 in their study, with reference to a former work by Brennan and Schwartz about the
evaluation of investments in natural resources ([23]). Basically, unpredictable events may be
described as Poisson processes, assumed to be reciprocally independent. They can be represented
in the model by introducing two increases of discount rate in Phase 1 and Phase 2. Therefore Eq. 22
and 24 will be updated as follows:

\[
26 \quad v(\tau_1) = E \left[ V(\tau_1) \cdot e^{-(\tau_1 + \lambda_2)\cdot t_2} \right. - \int_{0}^{\tau_2} I_2 \cdot e^{-(\tau_1 + \lambda_2)\cdot t} \cdot dt \left. \right| Q(\tau_1), K_2(\tau_1) \right]
\]

\[
27 \quad v(0) = E \left[ V(\tau_1) \cdot e^{-(\tau_1 + \lambda_1)\cdot t_1} \right. - \int_{0}^{\tau_1} I_1 \cdot e^{-(\tau_1 + \lambda_1)\cdot t} \cdot dt \left. \right| Q(0), K_1(0), K_2(0) \right]
\]

In the expressions \( \lambda_1 \) and \( \lambda_2 \) correspond to the intensities of Poisson processes describing the
unexpected damaging events during the two phases of research process.

The main criticality of the illustrated backward evaluation method is that analytical solution is not
feasible. Condition that expected NPV at the end of Phase 2 must be positive to go on with
medicine production would allow putting a constraint about reward share expected value, hence
about the product quality. However a closed form solution cannot be derived in correspondence to
the end of Phase 1, because of the conditional expectation dependence on random state variables.

Hsu and Schwartz proposed solution is a numerical approach to the problem, based on the
Longstaff and Schwartz algorithm for the estimation of American option value ([24]). A detailed
illustration of the main concepts of this approach is presented in the Appendix A.4. Basically, from
preliminary assumptions about problem deterministic parameters and the probability density
functions illustrated in the Appendices A.2 and A.3, simulations giving state variables are to be
done in large number, each one according to the logical sequence of Figure 3.1-2. Each group of
resulting values identifies a path, characterised by 0, \( \tau_1 \) and \( \tau_2 \) time nodes. Of course, for each path
\( \tau_1 \) and \( \tau_2 \) may have different values, because of their definition as random variables. For the same
reason expected final product quality at \( \tau_1 \) and \( \tau_2 \) may not be the same at different paths. Only at 0
time node it will have a known value, corresponding to analysis starting assumption. Concept of
simulation paths, with time nodes on the horizontal axis and expected quality on the vertical one,
is exemplified in Figure 3.2-1.
Expected NPV at research end time in the jth path, indicated as $\tau_j$, is defined as:

$$v(\tau^j) = e^{-\tau_j \cdot \gamma_3} \cdot \frac{1}{r} \cdot S_0 \cdot E[h_d(Q(\tau^j))] \cdot \left[ 1 - \frac{1}{(1 + r)^N_r} \right] \cdot \frac{I^j}{r_c} \cdot \left( 1 - e^{-\tau_j \cdot \gamma_3} \right)$$

In the expression the dependence of the new medicine reward share on product quality at $\tau_j$ is evidenced, but other terms are the same as in Eq. 19. Accordingly, it will be:

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

At the end of Phase 1 point estimates of the expected NPV of Eq. 22 for all paths are then derived. To this aim the simulated values of $\tau_2$ and results of Eq. 29 are used. For the generic jth path the point estimate will be:

$$\ddot{v}(\tau^j_1) = V(\tau^j) \cdot e^{-(\gamma_2 + \gamma_2)\tau_2} - \int_0^{\tau_2} I_2 \cdot e^{-(\gamma_2 + \gamma_2)t} \cdot dt$$

Point estimates for all the simulation paths shall be regressed onto a set of basis functions, according to the method illustrated in the Appendix A.4. In the current analysis state variables to consider are $Q(\tau^j_1)$ and $K_2(\tau^j_1)$, so a possible basis functions combination may be as shown in Eq. A.31. In this case, with the appropriate notation and by normalising the arguments of the functions to the initial assumptions about Phase 2 investment and final product quality, it will be:

$$\ddot{v}[Q(\tau^j_1), K_2(\tau^j_1)] \approx \sum_{k=0}^{M-1} \left\{ \alpha_k \cdot L_k[K_2(\tau^j_1)/K_2(0)] + \alpha_{k+M} \cdot L_k[Q(\tau^j_1)/Q(0)] \right\} +$$

$$+ \sum_{p=1}^{2} \sum_{q=1}^{2} \alpha_{2M+2p+q-3} \cdot L_p[K_2(\tau^j_1)/K_2(0)] \cdot L_q[Q(\tau^j_1)/Q(0)]$$
The coefficients can be derived according to the steps described in the Appendix A.4, for time node index \( i \) equal to 1. In the case under analysis \( Y_1 \) of Eq. A.30 will be a vector having as row elements the Eq. 30 point estimates evaluated for the \( N \) simulation paths. With the proposed set of basis functions the row of \( A_1 \) matrix corresponding to the generic \( j \)th path will be as follows:

\[
\begin{pmatrix}
L_0[K_2(\tau^1_1)/K_2(0)] \\
\vdots \\
L_{M-1}[K_2(\tau^1_1)/K_2(0)] \\
L_0[Q(\tau^1_1)/Q(0)] \\
\vdots \\
L_{M-1}[Q(\tau^1_1)/Q(0)] \\
L_1[K_2(\tau^1_1)/K_2(0)] \cdot L_1[Q(\tau^1_1)/Q(0)] \\
\vdots \\
L_2[K_2(\tau^1_1)/K_2(0)] \cdot L_2[Q(\tau^1_1)/Q(0)]
\end{pmatrix}^T
\]

Indeed the expression of Eq. 31 represents the \( j \)th element of a column vector with \( N \) rows, equal to the product between \( A_1 \) and the \( \Lambda_1 \) vector of \( \alpha_k \) coefficients, as defined in the Appendix A.4.

Previous results allow deriving an approximation of abandonment policy function at the end of Phase 1:

\[
\Omega[\nu(\tau^1_1)] \approx \Omega[\hat{\nu}[Q(\tau^1_1), K_2(\tau^1_1)]]
\]

Thus the present value of the project at that time node given the option to abandon, for the generic \( j \)th path, is:

\[
\hat{V}(\tau^1_1) = \Omega[\hat{\nu}[Q(\tau^1_1), K_2(\tau^1_1)]] \cdot \hat{\nu}[Q(\tau^1_1), K_2(\tau^1_1)]
\]
Going backward, to evaluate the policy function at the beginning of the research, the point estimate of expected NPV is required. It will be:

\begin{equation}
\hat{v}(\tau_0^j) = \hat{V}(\tau_1^j) \cdot e^{-(\tau_1^j + \lambda_1)} - \int_0^{\tau_1^j} 1 \cdot e^{-(t + \lambda_1)} dt
\end{equation}

This is the expression of point estimate for the generic \text{j}th path. However, the initial time node \( \tau_0 \) is equal to 0 for all the simulated paths, as exemplified in Figure 3.2-1. Therefore regression technique at this node simply reduces to approximate the expected present value to the arithmetic mean of the expressions of Eq. 35 for all the paths:

\begin{equation}
\hat{v}(0) = \frac{1}{N} \sum_{j=0}^{N-1} \hat{v}(\tau_0^j)
\end{equation}

Policy function is simply the following:

\begin{equation}
\Omega[v(0)] \approx \Omega[\hat{v}(0)]
\end{equation}

Having defined the abandonment policy functions at all time nodes it is now possible to evaluate the expected NPV of the medicine research project by applying the Monte Carlo method. Results from previous simulations will be used. Therefore the expression of project expected value driving the innovator’s decision whether to start the research or not is:

---

* Use of \( \tau_0 \) 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.
The terms of the expression are those defined in the previous steps.

Figure 3.2-1: Simulation paths and time nodes concepts
4 Numerical examples

4.1 Assumptions

The goal of the numerical simulations illustrated in the following paragraphs is to verify the Pogge’s incentive system effectiveness with diseases having different health impacts. Furthermore, it may be interesting to compare resulting incentives for drug and vaccine development.

Simulations have been done by applying the aforesaid model to four different cases. The former two cases take in account the development of a drug, aimed to healing people that have contracted the disease of interest. Pogge’s incentive system results are found for a largely spread disease like malaria and a less spread although harmful disease like Dengue fever. In the latter two cases the new medicine is a vaccine, so evaluations are done considering the benefits of immunization of still healthy people. Health fund is supposed to have an annual endowment of 6 billion Euros, about the amount proposed by Hollis and Pogge in their joint work as the minimum size\textsuperscript{10} ([6]). Therefore it is reasonable to assume that discovered medicines for only some global spread diseases are rewarded. Specifically, the following diseases are considered:

- Tuberculosis
- HIV
- Malaria
- Dengue fever

\textsuperscript{10} In the following the money figures are expressed in Euros, although original values, in referred literature papers, are in USD. This means an increase of about 1.36 times. However, this is not a problem, considering that some reference works date back to some years ago, so cost data in USD should be updated anyway.
For an at least preliminary characterisation of the therapeutic improvement due to the introduction of new remedies, the average disease burden per capita can be estimated, considering the available data about GDB and global diffusion. This evaluation can be only approximative, because diseases real effects depend on several factors. For instance, a malaria infected patient living in an African country will probably find more health troubles than a European or American traveller that has contracted the disease in the same place but can receive the necessary cures in his own nation. However, in a worldwide assessment of health benefits of a drug or a vaccine use of aggregate or average parameters is inevitable. From information reported in the 2008 GDB report by WHO the results of Table 4.1-1 are found ([9]).

Simulations with the analytical model require the definition of several parameters. Possible values are listed in Table 4.1-2. According to Hollis and Pogge work, reward period is assumed equal to ten years. Nominal durations of research phases and production plant upgrade and investment rates are derived from pharmaceutical industry typical values. Model specific parameters, like the investment volatilities or the final quality delay terms, come from the works of Hsu and Schwartz.

<table>
<thead>
<tr>
<th>Disease</th>
<th>GDB</th>
<th>Diffusion</th>
<th>Average DALYs per capita</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>33,976,025</td>
<td>241,340,106(^{11})</td>
<td>0.14</td>
</tr>
<tr>
<td>HIV AIDS</td>
<td>58,512,844</td>
<td>31,395,346(^{12})</td>
<td>1.86</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>34,216,721</td>
<td>14,000,000(^{13})</td>
<td>2.44</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>669,648</td>
<td>8,950,954(^{14})</td>
<td>0.075</td>
</tr>
</tbody>
</table>

Table 4.1-1: Diffusion, global and average disease burden pro capita for the considered diseases

---

\(^{11}\) Incidence is considered, intended as episodes of illness.

\(^{12}\) Prevalence is considered. All several viral subtypes and illness stages are included.

\(^{13}\) Prevalence is considered.

\(^{14}\) Incidence is considered, intended as episodes of illness due to several Dengue fever subtypes.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 duration initial assumption [years]</td>
<td>$\tau_1(0)$ 3</td>
</tr>
<tr>
<td>Phase 2 duration initial assumption [years]</td>
<td>$\tau_2(0)$ 6</td>
</tr>
<tr>
<td>Scaling up of production plants time [years]</td>
<td>$\tau_3$ 1</td>
</tr>
<tr>
<td>Reward period [years]</td>
<td>$T_R$ 10</td>
</tr>
<tr>
<td>Number of rewarded years</td>
<td>$N_R$ 10</td>
</tr>
<tr>
<td>Health fund annual endowment [M€]</td>
<td>$S_0$ 6000</td>
</tr>
<tr>
<td>Phase 1 investment rate [M€/year]</td>
<td>$I_1$ 20</td>
</tr>
<tr>
<td>Phase 2 investment rate [M€/year]</td>
<td>$I_2$ 15</td>
</tr>
<tr>
<td>Production infrastructure building or scaling up investment rate [M€/year]</td>
<td>$I_3$ 50</td>
</tr>
<tr>
<td>Phase 1 investment volatility [M€/year]</td>
<td>$\sigma^2_1$ 5</td>
</tr>
<tr>
<td>Phase 2 investment volatility [M€/year]</td>
<td>$\sigma^2_2$ 10</td>
</tr>
<tr>
<td>Correlation factor between Phase 1 and 2 completion cost Wiener processes</td>
<td>$\rho$ 0.1</td>
</tr>
<tr>
<td>Discount rate on annual base</td>
<td>$r$ 4%</td>
</tr>
<tr>
<td>Additional continuous discount rate for Phase 1 unpredictable events</td>
<td>$\lambda_1$ 1%</td>
</tr>
<tr>
<td>Additional continuous discount rate for Phase 2 unpredictable events</td>
<td>$\lambda_2$ 1%</td>
</tr>
<tr>
<td>Exponent of delay term in mean of expected final quality at Phase 1 end</td>
<td>$\eta_{\mu,1}$ 0.2</td>
</tr>
<tr>
<td>Exponent of delay term in mean of expected final quality at Phase 2 end</td>
<td>$\eta_{\mu,2}$ 0.05</td>
</tr>
<tr>
<td>Exponent of delay term in variance of expected final quality at Phase 1 end</td>
<td>$\eta_{\sigma,1}$ -0.2</td>
</tr>
<tr>
<td>Exponent of delay term in variance of expected final quality at Phase 2 end</td>
<td>$\eta_{\sigma,2}$ -0.05</td>
</tr>
<tr>
<td>Variance parameter in expected final quality at Phase 1 end</td>
<td>$s(\tau_1)$ 0.05</td>
</tr>
<tr>
<td>Variance parameter in expected final quality at Phase 2 end</td>
<td>$s(\tau_2)$ 0.02</td>
</tr>
<tr>
<td>Estimate of final product efficacy at research beginning</td>
<td>$Q(0)$ 0.5</td>
</tr>
<tr>
<td>Other incentivized products quality mean</td>
<td>$\mu_{Q_{oth}}$ 0.5</td>
</tr>
<tr>
<td>Other incentivized products quality variance</td>
<td>$\sigma^2_{Q_{oth}}$ 0.01</td>
</tr>
</tbody>
</table>

Table 4.1-2: General parameters for simulations
4.2. Drug case

Values of two projects aimed to develop new drugs respectively for malaria and Dengue fever have been calculated according to the approach illustrated in previous sections. The same time pattern distribution is assumed for all the fund rewarded medicines, so that Eq. 3 in par. 2.2 is used for the evaluation of reward shares. Annual reference values of disease burdens are supposed 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 has been done. Malaria has the higher GDB, so it is reasonable to expect that it will correspond to the more rewarding project. Evolution of expected final quality of the drug and time nodes, hence duration of phases, for the simulated paths is presented in Figure 4.2-1. The diagram evidences the different values of $\tau_1$ and $\tau$ for the paths, as well as the different expected values of product quality. Approximation of expected NPV at $\tau_1$ with the Longstaff and Schwartz method is shown in Figure 4.2-2. In the left diagram expected NPV estimates for the simulation paths, each one corresponding to a quality value on the horizontal axis, are compared to the values of the approximating polynomial function. The right diagram is similar, but with Phase 2 expected completion cost as the independent variable. Approximation fitting to estimates is good, thanks to the large number of paths considered for the simulation. Finally, profile of the approximating function versus the two state variables is shown in Figure 4.2-3. Differently from the diagrams of Figure 4.2-2 the profile has been obtained by considering all the possible combinations of state variables values, not only those resulting from the simulations. It is interesting to note that expected NPV at $\tau_1$ has high values, except for a small region corresponding to low quality and high Phase 2 completion costs. Project value at the beginning, evaluated according to Eq. 38, is equal to 7,841 M€. Therefore the innovator will undoubtedly find convenient to undertake the research and development of a new anti-malaria drug.
The situation changes for Dengue fever, having a lower worldwide health impact. Indeed, although it is less harmful than HIV or malaria, Dengue fever is not rare, nor it is a lesser disease. It may degenerate towards complications like hemorrhagic fever or shock syndromes. Furthermore, factors like progressive urbanization in tropical areas, population growth, international travelling and global warming have probably facilitated the disease spread in the last decades. Evolution of expected final quality of the drug and time nodes instants is presented in Figure 4.2-4. Correspondence between approximating function and estimates of expected NPV at $\tau_1$ is shown in Figure 4.2-5. As for malaria, data fitting is good although, as expected because of the lower GDB, resulting values are lower. Profile of NPV at $\tau_1$ for different combinations of $Q(\tau_1)$ and $K_2(\tau_1)$ is reported in Figure 4.2-6. It can be noted that there are more combinations corresponding to non positive NPV values than in Figure 4.2-3. By applying Eq. 38 the expected NPV at project beginning results equal to 6.427 M€. It is considerably lower than the resulting value in the case of malaria. If uncompensated costs were added, proportionally to the number of patients or medicine distributed quantities, they would probably lead to a negative value.

It is important to remember that, to induce a pharmaceutical corporation or research institute to take the long and expensive path to the discovery of a new medicine, a weakly positive estimated NPV is not enough. Even a small error in the definition of the numerical parameters of the simulation, due to incomplete information, could easily reverse the result, leading to unexpected financial losses for the innovator. This eventuality is much less probable if simulations deliver a high value, as in malaria example. However, it is difficult to establish a less trivial reference threshold than the null value. To define an enough comfortable margin, a possible rule of thumb could be to take as threshold the sum of typical Phase 1 and 2 investment costs, namely $K_1(0)$ and $K_2(0)$, or a percentage of it. Anyway, previous results confirm that development of a new drug for the disease having a larger GDB is much more rewarding.
Figure 4.2-1: Expected final quality and time nodes for different paths (malaria drug case)

Figure 4.2-2: Estimated and approximated $v(\tau_1)$ as state variables function (malaria drug case)
Figure 4.2-3: NPV at $\tau_1$ approximating function vs. $Q(\tau_1)$ and $K_2(\tau_1)$ (malaria drug case)

Figure 4.2-4: Expected final quality and time nodes for different paths (Dengue drug case)
Figure 4.2-5: Estimated and approximated $v(\tau_1)$ as state variables function (Dengue drug case)

Figure 4.2-6: NPV at $\tau_1$ approximating function vs. $Q(\tau_1)$ and $K_2(\tau_1)$ (Dengue drug case)
4.3. Vaccine case

Pogge’s system effectiveness for vaccines can be tested by using the indications from existing studies about future products development. For HIV, malaria and tuberculosis global coverage progression can be modelled according to demand forecasts that are illustrated in the Appendix A.1. Unfortunately no comparable data are available for Dengue fever, so it is supposed that global coverage of a new vaccine for that disease will follow the DTP3 immunization time pattern, having the annual infant surviving cohort of 130 millions people as worldwide target population.

As in previous paragraph incentives to the development of new vaccines for malaria and Dengue fever have been considered. With the coverage time profiles described in the Appendix A.1, reward share for each vaccine is evaluated by using Eq. 2. Time profiles of annual therapeutic improvements due to the vaccines for the four diseases are shown in Figure 4.3-1 and Figure 4.3-2. It is worthwhile that difference between malaria and dengue is apparently much less pronounced than in terms of disease burdens.

Simulation of 10,000 evolution paths has been done for both the diseases under analysis. For a malaria vaccine expected final quality values and corresponding time nodes for the simulated paths are reported in Figure 4.3-3. Estimated and approximated NPV at the end of Phase 1 present a good correspondence, as shown in Figure 4.3-4. Approximating function for different combinations of $Q(\tau_1)$ and $K_2(\tau_1)$ is represented in Figure 4.3-5. Expected NPV at project beginning is evaluated by applying Eq. 38. It results equal to 373.545 M€.

For a Dengue vaccine results of simulations are shown in Figure 4.3-6, Figure 4.3-7 and Figure 4.3-8. Expected NPV at the beginning of research process is 238.271 M€. Although lower than the malaria vaccine value, there is not a high difference between the two results. This outcome is plausible, considering that the supposed health benefits profiles for the two vaccines have fairly similar values over the reward period. According to the proposed model therapeutic improvement depends on individual health damage and size of target population of immunization campaigns.
Figure 4.3-1: Health benefit time profiles for malaria and HIV vaccines
Figure 4.3-2: Health benefit time profiles for tuberculosis and Dengue vaccines
Figure 4.3-3: Expected final quality and time nodes for different paths (malaria vaccine case)

Figure 4.3-4: Estimated and approximated $v(\tau_1)$ as state variables function (malaria vaccine case)
Figure 4.3-5: NPV at $\tau_1$ approximating function vs. $Q(\tau_1)$ and $K_2(\tau_1)$ (malaria vaccine case)

Figure 4.3-6: Expected final quality and time nodes for different paths (Dengue vaccine case)
Figure 4.3-7: Estimated and approximated $v(\tau_1)$ as state variables function (Dengue vaccine case)

Figure 4.3-8: NPV at $\tau_1$ approximating function vs. $Q(\tau_1)$ and $K_2(\tau_1)$ (Dengue vaccine case)
5 Conclusions

Current patent system inadequacy to promote the development of new medicines for the diseases that mainly affect low income countries is nowadays acknowledged and reform is loudly invoked by several parties. The peculiarity of the proposal of Pogge is that it does not pretend to change or suppress the existing incentive system, although the author is primarily moved by the deep consciousness of its inherent injustice. By conceiving the alternative system as a complement rather than a substitute, Pogge is confident that the main corporate players of pharmaceutical market will cooperate to its success. Undoubtedly the proposal has the potential of overcoming the traditional system inadequacy to promote the development of remedies to neglected pathologies. Nevertheless, detailed definition of reward system needs further clarification. According to the previously illustrated results, diseases with more severe health damages per capita and larger worldwide burdens would apparently be favoured. Indeed Pogge’s proposal is primarily aimed to promote the discovery of new medicines for this kind of pathologies. However, it is important not to neglect those diseases that affect large segments of world population, mainly in poorer areas, although less painful than spread and harmful pathologies like tuberculosis or HIV. A careful design of all the operative aspects of reward system is hence necessary for a successful implementation of the proposal.

Of course Pogge’s proposal is not the only possible solution to the defects of traditional pharmaceutical patent system. Research initiatives of no-profit organizations and philanthropic institutions, like the Gates foundation, as well as governmental programmes, both at national and international level, represent an alternative option. Resulting efforts in developing new medicines for harmful pathologies like HIV/AIDS are remarkable. All these initiatives are implemented out of the pharmaceutical innovation incentive system based on intellectual property rights. This option resembles to the promotion of basic scientific research, not directly targeted to the development of marketable products. However, Pogge’s idea deserves further analysis efforts because of its worthwhile potential.
Appendix

A.1 Global diffusion and therapeutic effects over time

Worldwide distribution of new vaccines and drugs is inevitably gradual. While in wealthy countries it is a relatively easy task, less developed areas usually offer insufficient transport infrastructures and networks, as well as poor public health services. Under the current patent system this latter factor has probably contributed to the fragmentation of local markets, hence weakening the strength of the customers in the face of pharmaceutical corporations and facilitating the imposition of high sale prices.

The definition of a time profile of global coverage by a new vaccine can be done by using data from the past worldwide immunization campaigns. A frequently used reference is the vaccination against diphtheria, tetanus and pertussis promoted in the frame of the Expanded Program on Immunization (EPI). The EPI was started with the objective to vaccinate children throughout the world, therefore having a very large number of candidate beneficiaries. Specifically, target population was the worldwide annual surviving infants’ cohort, estimated to 130 million individuals. DTP3 immunization campaign has lead from a target population global coverage of 20% in 1980 to a level of 82% in 2009, but with a more sensible increase in the first ten years, as shown in Figure A.1-1. It is to be noted that the program enhanced the effort for worldwide immunization against the three diseases but a not negligible vaccinated share of annual target population already existed before it, mainly concentrated in affluent countries. Although considerable, the overall coverage increment from the beginning to the end of the thirty years period due to the program amounted to about 60% only of the target population. It is reasonable to assume a similar global distribution time pattern for a new product developed under the Pogge proposed system, if no more specific indication is available.

From DTP3 immunization campaign historical data the following interpolating function is derived, with time variable t expressed in years:

\[
A.1 \quad D(t) = a_0 \cdot [1 - \exp(-a_1 \cdot t)]
\]
The $a_0$ and $a_1$ coefficients result respectively equal to 0.602 and 0.139, assuming that function represents the percentage of annual target population coverage. A comparison between the interpolating function and DTP3 coverage data is shown in Figure A.1-2. It is important to remember that the formula describes the progressive growth of immunized share of annual target population, not the total number of vaccinated individuals at a given year. The latter is a cumulative parameter and can be obtained by integrating the expression of Eq. A.1 over a specific period, taking into account the annual target population size.

The number of immunized people at $t$ years after the campaign beginning is then:

\[ N_V(t) = N_{V0} \cdot D(t) = N_{V0} \cdot a_0 \cdot [1 - \exp(-a_1 \cdot t)] \]

$N_{V0}$ is the vaccination annual target population size in millions individuals. It is assumed not to change over time, at least during the considered ten years period. The expression is important for the evaluation of health improvement due to a new vaccine. Disease burden will correspond to an average DALY value per person. Its product by the number of immunized individuals will represent vaccine therapeutic benefits. It will be:

\[ G_V(t) = g \cdot N_V(t) = G_{V0} \cdot D(t) \]

In the formula $g$ is the average DALY per person for the disease of interest and $G_{V0}$ is the total avoided disease burden for the annual target population.

Although often recalled in specialized literature, DTP3 immunization program is not the only possible reference. Another pattern is represented by the global coverage temporal profile of Hepatitis B vaccination. The progressive diffusion of third dose inoculation of Hepatitis B vaccine from 1990 to 2009 is shown in Figure A.1-3. Differently from DTP3, here a large global coverage has been achieved in only twenty years. However, the first decade was characterised by a rather low penetration of the vaccine. Only after 1999 there was a boost of worldwide inoculation, with a coverage increase from 15% to about 70%. Other references can be found in studies about future vaccines. For instance, a Boston Consulting Group study sponsored by Malaria Vaccine Initiative...
in 2005 contains useful indications about vaccine uptake progression ([26]). Demand forecast on a
ten year period from 2015 to 2025, without funding constriction, for products respectively with
30%, 50% and 80% efficacy, is shown in Figure A.1-4. These data allow deriving a formula for the
demand as a function of vaccine quality. For the product with an expected efficacy of 50% an
interpolation function is derived. It is more complicated than the approximating expression for
DTP3 immunization campaign results:

\[ N_{V,M}(t) = b_0 + b_1 \cdot \tanh(t) + b_2 \cdot e^{b_3 \cdot t} \]

From the report available data \( b_0, b_1, b_2 \) and \( b_3 \) respectively result equal to -6.419, 8.598, 6.419 and
0.216\(^{15}\). Interpolated profile is shown in Figure A.1-5.

In the same way, a 2006 study prepared for BIO Ventures for Global Health (BVGH) provides
useful indications about global demand for new vaccines against tuberculosis ([27]). Specifically,
the document presents the estimation of progressive distribution of a new vaccine substituting the
conventional product based on Bacillus Calmette-Guérin (BCG) immunization. Indeed resulting
profile is not much different from the DTP3-like one, as shown in Figure A.1-6. A similar
approximating function can be used:

\[ N_{V,TB}(t) = c_0 \cdot [1 - \exp(-c_1 \cdot t)] \]

Interpolated profile is presented in Figure A.1-7. Here \( c_0 \) is 108.828 and \( c_1 \) is 0.145.

The assumption that data are referred to a funding unconstrained demand may translate into the
assumption that sale price is equivalent to marginal production and distribution cost. A similar
approach has been adopted by Hsu and Schwartz ([20]). The authors define the vaccine demand
starting from the study of Esparza et al. about the uptake of a HIV/AIDS vaccine ([28]). As in the
previously mentioned work about malaria, the vaccine global demand depends on the efficacy.
Probable uptake is estimated to be only a small fraction of global demand, from about 19% with a

\(^{15}\) Indeed interpolating algorithm would give -6.122 for the first coefficient, but it has been set to -6.419 to
have null coverage at year 0.
low efficacy product to about 38% with a high efficacy one. However, Hsu and Schwartz do not suppose that vaccine diffusion over time would occur according to DTP3-like or alternative profiles, related to former immunization programs. They simply divide the estimated global vaccine uptake by five years i.e. the required period for a global immunization campaign according to Esparza, hence considering the average annual number of actual inoculations, provided that sale price is the marginal production cost only. Indeed it is more realistic to assume that vaccine uptake would follow a less trivial time pattern, as fraction of global needs as evaluated in the study by Esparza or other works about this issue. For instance, the global demand forecast for a preventive HIV vaccine has been analysed in an International AIDS Vaccine Initiative (IAVI) working paper in 2007 ([29]). Annual number of immunization courses for a vaccine has been assessed for different estimated efficacies. Results for a 50% effective product are presented in Figure A.1-8. In this case interpolating function is slightly different from the usual DTP3-like one that has probed to be appropriate for tuberculosis global demand forecast approximation:

\[
A.6 \quad N_{V,HIV}(t) = d_0 \cdot [1 - \exp(-d_1 \cdot t^{d_2})]
\]

The three coefficients \(d_0\), \(d_1\) and \(d_2\) are respectively equal to 80.74, 0.022 and 2.37. Interpolating function profile and forecast data are shown in Figure A.1-9. Although fitting is less good than in other cases, it is considered acceptable for the first ten years that is the health fund proposed reward period.

Previous considerations are useful for the modelling of therapeutic improvement due to a new vaccine. Situation is different for a drug to be administered to sick people only. In this case the annual target population consists of the number of disease cases or episodes, derivable from the international health statistics. For instance, the WHO report of 2008 about global burden of diseases illustrates the diffusion of major pathologies in the world ([9]). An important parameter is the prevalence, indicating the number of individuals who have a specific illness at a given moment in the survey year. Worldwide prevalence data are reported for severe diseases like tuberculosis and HIV/AIDS, currently lacking of effective remedies. In other cases WHO document only reports the incidence i.e. the number of new cases occurring in the survey year, although information about diseases diffusion can be derived from different sources. These data are quite useful for the current analysis, but it is important to remember that they are referred to a specific period.
Diffusion of a disease could change in the years, also in absence of new medical discoveries, for hygienic, environmental or socio-economic reasons. For instance, new resistant viral or bacterial subtypes could appear, or the general economic development could improve life conditions and therefore public health. Although projections of expected future prevalence and incidence of the most important diseases have been developed, their reliability is limited.

The aforementioned considerations provide a reference for the drug global need at the beginning of reward period. However, definition of candidate recipient population over time depends on several assumptions. Drug administration to patients could be continuous, at least until when the disease persists. Some infections could be ineradicable, but drugs could improve the health of the patients, preventing the occurrence of complications and allowing them to live an almost normal life. This is the currently occurring situation with HIV/AIDS anti-retroviral medicines. Those receiving the drug in a given year will continue to receive it the following years and more recipients will add over time, due to both the medicine progressive distribution and the appearance of new patients. The therapeutic benefit of drug administration, intended as the procured relief from sickness, will be equivalent to the product of drug efficacy and disease burden of recipient population. A different situation occurs if the new drug can really eradicate the disease, instead of simply reducing its negative health effects. In this case therapeutic benefit corresponds to the removed disease burden from recipient population, depending on product efficacy. In the following years drug distribution will reach the still untreated patients, as well as the new affected individuals.

It is interesting to note that all previous considerations could be not so much influent for reward evaluation, provided that all new medicines have the same coverage temporal profile. Furthermore, basic model assumes that all production and distribution costs are recovered by medicine sale price, so no uncompensated costs are considered. However, although reasonable, such conditions may not occur in specific cases.
Figure A.1-1: Global coverage of DTP3 immunization (Credits: [25])

Figure A.1-2: Global coverage time profile approximation of DTP3 normalized data pattern
Figure A.1-3: Global coverage of HepB3 immunization (Credits: [25])

Figure A.1-4: Global demand forecast of a malaria vaccine (Credits: [26])
Figure A.1-5: Global coverage time profile approximation of a 50% effective malaria vaccine

Figure A.1-6: Global demand forecast of a BCG-substitute tuberculosis vaccine (Credits: [27])
Figure A.1-7: Global coverage time profile approximation of a BCG-substitute tuberculosis vaccine

Figure A.1-8: Global demand forecast of a 50% effective HIV vaccine (Credits: [29])
A.2 Statistical characterisation of completion times

Phase 1 and Phase 2 lengths are random variables that can be characterised by considering their relation to the expected completion costs. Each completion time is defined as the first instant the stochastic process describing the phase expected residual cost hits the 0 level i.e. becomes null. As explained in par. 3.1, expected completion costs are defined as Brownian motions with drift. Statistical distribution of their passage or hitting times will characterise the corresponding phase length\textsuperscript{16}. Probability density functions for Phase 1 and Phase 2 completion times will then be the following:

\begin{align}
\Phi_1(\tau_1) &= \frac{K_1(0)}{\sqrt{2 \cdot \pi \cdot \tau_1^3 \cdot \sigma_1^2}} \cdot \exp\left\{-\frac{[K_1(0) - I_1 \cdot \tau_1]^2}{2 \cdot \sigma_1^2 \cdot \tau_1}\right\} \\
\Phi_2(\tau_2) &= \frac{K_2(\tau_1)}{\sqrt{2 \cdot \pi \cdot \tau_2^3 \cdot \sigma_2^2}} \cdot \exp\left\{-\frac{[K_2(\tau_1) - I_2 \cdot \tau_2]^2}{2 \cdot \sigma_2^2 \cdot \tau_2}\right\}
\end{align}

\textsuperscript{16} Theoretical frame and details are reported in par. 2.6 and par. 3.5 of [21].
As shown in the work of Hsu and Schwartz, previous results can be used to derive the statistical density of $K_2(\tau_1)$, that is the only unknown cost parameter of interest ([20]). During Phase 1 unexpected research costs can be expressed as:

A.9 \[ \Psi_1 = K_1(0) - I_1 \cdot \tau_1 \]
A.10 \[ \Psi_2 = K_2(0) - K_2(\tau_1) \]

It is interesting to note that the former expression is the difference between Phase 1 cost expectation at its beginning and actual resulting cost at its completion, when all the corresponding research activities have been performed. Instead the latter represents the revision of Phase 2 expected costs, depending on the events occurring during Phase 1 progress but before Phase 2 actual beginning. By definition it will then be:

A.11 \[ \Psi_1 = \int_0^{\tau_1} \sigma_1 \cdot dW_1 \]
A.12 \[ \Psi_2 = \int_0^{\tau_1} \sigma_2 \cdot dW_2 \]

Some manipulations are here possible, considering the par. 3.1 assumption that $dW_1$ and $dW_2$ are correlated and indicating their instantaneous correlation as $\rho \cdot dt$. Therefore it is possible to decompose $dW_2$ in a combination of $dW_1$ and another Brownian motion $dZ_2$, orthogonal to the latter. Thus $\Psi_2$ may be expressed as:

A.13 \[ \Psi_2 = \frac{\sigma_2}{\sigma_1} \cdot \rho \cdot \Psi_1 + \sigma_2 \cdot \sqrt{1 - \rho^2} \cdot Z_2(\tau_1) \]

In the expression $Z_2(\tau_1)$ is a normal random variable with variance $\tau_1$ and null mean. By substituting $\Psi_2$ definition of Eq. A.13 in Eq. A.10 it is finally possible to explicit $K_2(\tau_1)$:
A.14 \( K_2(\tau_1) = K_2(0) - \frac{\sigma_2}{\sigma_1} \cdot \rho \cdot [K_1(0) - I_1 \cdot \tau_1] - \sigma_2 \cdot \sqrt{1 - \rho^2} \cdot Z_2(\tau_1) \)

Of course the expression does not give a defined value, because of the stochastic nature of the terms. Nevertheless, it allows a statistical characterisation of \( K_2(\tau_1) \), that may be defined as a conditionally normal variable, whose mean and variance are derived from it:

A.15 \( \mu_{K_2(\tau_1)} = E[K_2(\tau_1)] = K_2(0) - \frac{\sigma_2}{\sigma_1} \cdot \rho \cdot [K_1(0) - I_1 \cdot \tau_1] \)

A.16 \( \sigma^2_{K_2(\tau_1)} = \text{Var}[K_2(\tau_1)] = \sigma^2_2 \cdot (1 - \rho^2) \cdot \tau_1 \)

so that the \( K_2(\tau_1) \) density function is\(^{17}\):

A.17 \( \Phi_{K_2(\tau_1)}[K_2(\tau_1)] = \frac{1}{\sqrt{2 \cdot \pi \cdot \sigma^2_{K_2(\tau_1)}}} \cdot \exp\left\{ -\frac{[K_2(\tau_1) - \mu_{K_2(\tau_1)}]^2}{2 \cdot \sigma^2_{K_2(\tau_1)}} \right\} \)

Previous results are fundamental to perform numerical simulations for the analysis of pharmaceutical research project sustainability. Values of completion times \( \tau_1 \) and \( \tau_2 \) and expected cost \( K_2(\tau_1) \) can be derived by using the respective density functions in some logical steps. Specifically, a value for \( \tau_1 \) is first drawn for the density function of Eq. A.7, so allowing the evaluation of \( K_2(\tau_1) \) mean and variance from Eq. A.15 and A.16. These parameters are then substituted into density function of Eq. A.17, allowing the extraction of a value for \( K_2(\tau_1) \). Finally, the latter is substituted into density function of Eq. A.8, to draw a value for \( \tau_2 \). All these values identify one of the possible random paths characterising the evolution of the research process, given its stochastic features.

\(^{17}\) Note that here the whole \( K_2(\tau_1) \) term is the random variable.
A.3 The expected quality of research result

Quality or efficacy of a new medicine may be adequately represented as a random variable with Beta distribution. Generic Beta probability density function is the following:\textsuperscript{18}

\begin{equation}
A.18 \quad f_Q(Q) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha) \cdot \Gamma(\beta)} \cdot Q^{\alpha-1} \cdot (1 - Q)^{\beta-1} \quad \text{for } 0 \leq Q \leq 1
\end{equation}

where \( \alpha \) and \( \beta \) depend on mean \( \mu_Q \) and variance \( \sigma_Q^2 \) of the distribution:

\begin{align*}
A.19 \quad \alpha &= \mu_Q \cdot \left[ \frac{\mu_Q \cdot (1 - \mu_Q)}{\sigma_Q^2} - 1 \right] \\
A.20 \quad \beta &= (1 - \mu_Q) \cdot \left[ \frac{\mu_Q \cdot (1 - \mu_Q)}{\sigma_Q^2} - 1 \right]
\end{align*}

As shown in par. 2.2, efficacies of pharmaceutical remedies developed in the frame of Pogge system can be modelled as Beta distributed random variables. However, in the evaluation of expected return from a specific medicine development, the density function should have a dependence on the state variables at the key moments of research process, namely the beginning of Phase 1, the end of Phase 1 (or beginning of Phase 2) and the end of Phase 2, respectively corresponding to 0, \( \tau_1 \) and \( \tau \) time instants.

The solution proposed by Hsu and Schwartz consists of introducing mean and variance dependence on expected final quality of the medicine, according to definition of par. 3.1, and the expected phase length at previous step. Expressions are the following:

\textsuperscript{18} Details for Beta density properties are illustrated in [11].
In the equations $E_{\tau_{i-1}}$ is the expected value of $\tau_i$ at $\tau_{i-1}$, where $\tau_i$ is the research phase completion time and may be equal to $\tau_1$ or $\tau_i$. $\tau_{i-1}$ is the time instant reference for the expectation about $\tau_i$ and will be 0 or $\tau_1$.

The two exponents in mean and variance formulas are introduced to shape the dependence on the difference between phase actual completion time and its expectation at previous reference time. If the exponents were null, mean and variance would not directly depend on phase completion delay. Mean at $\tau_i$ would be equal to the expected final product quality at $\tau_{i-1}$ and variance would reduce to a combination of mean itself and the $s(\tau_{i-1})$ parameter, namely:

$$\sigma^2_{Q_d}(\tau_i)_{\eta_{s,i} = 0} = \mu_{Q_d}(\tau_i) \cdot [1 - \mu_{Q_d}(\tau_i)] \cdot s(\tau_{i-1})$$

Instead, if the exponents are not null, mean and variance will depend on the ratio between $\tau_i$ and $E_{\tau_{i-1}}$. This dependence may be interpreted as a characterisation of learning process occurring during the research of that medicine. A longer phase could improve the developer’s knowledge about the product features, therefore enhancing the expectations about its final quality and reducing the degree of uncertainty about it during the research activities. However, the opposite could also occur. Phase completion delay could increase the confusion about the probable research outcome, worsening the final product quality expectations.

Examples of mean and variance dependences on phase completion delay are respectively shown in Figure A.3-1 and Figure A.3-2. Considered values for Eq. A.21 and A.22 parameters are the following:
\[ Q(\tau_{i-1}) = 0.5 \]
\[ \eta_{\mu,i} = 0.2 \]
\[ \eta_{\sigma,i} = -0.2 \]
\[ s(\tau_{i-1}) = 0.05 \]

Values for the exponents and \( s(\tau_{i-1}) \) have been found in a 2003 issue of Hsu and Schwartz work. Mean is compared to its own expression with null \( \eta_{\mu,i} \) i.e. the final quality expectation at previous time. As for variance, reference level is that defined in Eq. A.23. Independent variable is relative phase completion delay i.e. \( (\tau_i - E_{e,i}[\tau_i]) - E_{e,i}[\tau_i] \).

With previous assumptions, if actual phase length exceeds its former expectation, mean becomes higher than earlier expected final quality. This could be interpreted as a consequence of learning occurring during the research activities. In the example, a prolonged phase will improve the developer’s knowledge about the medicine, so enhancing the mean final efficacy. In the same way, variance diminution under the reference level of Eq. A.23 would express the lesser statistical dispersion of possible efficacy values, thanks to a longer learning process. Of course different results will be obtained if other settings of the two exponents are used.

It is noticeable that in the 2007 issue of their work Hsu and Schwartz have more simply assumed that mean and variance exponents for both the phases are null. This would remove the dependence on phase completion delay that indeed represents a critical aspect of the expected final quality characterisation, limiting the research time evolution effect to the introduction of former step expected quality in mean definition.
Figure A.3-1: Mean of expected product quality vs. phase completion relative delay

Figure A.3-2: Variance of expected product quality vs. phase completion relative delay
A.4 The Longstaff and Schwartz least square method solution

In a work of 2001 Longstaff and Schwartz describe a least square method to estimate the value of American options by simulation ([24]). Financial options are generally classified depending on the date of exercise. European style options may be exercised only at the expiry date of the option, while American options may be exercised at any time before it. Indeed there are many other option styles, with different early exercise criteria. For instance, with Bermudan options, so named because they are an intermediate style between the American and European ones, the right to exercise is set at a discrete number of times.

In real world the holders of an option cannot be sure whether to exercise it or not is convenient. Option future value is at least partially unpredictable. Many factors generally determine it, so traditional evaluation techniques, like the finite difference method, do not appear practicable. Longstaff and Schwartz propose a numerical simulation method to individuate the optimal conditions to exercise the option. At any exercise time the holder of the option compares the payoff from immediate exercise with the expected payoff from continuation. If the former is higher the option will be exercised, otherwise it will be retained. Therefore the optimal exercise strategy depends on the conditional expectation of the payoff from retaining the option. The method consists of estimating the conditional expectation by the regression of the payoffs that would be realized from continuation on functions of the state variables characterising the option value in the course of the time. These functions form the basis for the regression and least squares technique is used to determine the best fitting. This will require the simulation of a large number of different time paths, each one corresponding to a set of state variables values. The fitted values thus represent an estimate of the conditional expectation function. To obtain the complete characterisation of optimal exercise strategy, conditional expectation function shall be estimated for each exercise date. In their work the authors call the aforedescribed technique the least squares Monte Carlo approach.

Longstaff and Schwartz method has been addressed by several authors. In particular, A. R. Choudhury et al. provide several useful indications for its practical implementation ([30]). For a generic path $\omega$ the option continuation value at a given time before the expiration can be approximated as a finite linear combination of a set of measurable basis functions:
A.24 \( F(\omega, t_1) \approx \sum_{k=0}^{M-1} \alpha_k \cdot L_k[S(t_1, \omega)] \)

M is the number of combination elements. In the financial options case \( S \) represents the underlying asset price.

Different basis functions may be used. One possible choice is a set of weighted Laguerre polynomials:

A.25 \[ L_k(X) = \left[ \frac{e^X}{k!} \cdot \frac{d^k}{dX^k} \left( X^k \cdot e^{-X} \right) \right] \cdot e^{-\gamma X} \]

In the expression the argument \( X \) corresponds to the state variable.

Least square regression is aimed to find the coefficients \( \alpha_k \) of Eq. A.24. Assuming that \( N \) is the number of simulated time paths, an \( N \times M \) matrix for the \( i_{th} \) time node is defined, with the following elements:

A.26 \( A_i(j, k) = L_k[S(t_1, \omega_j)] \)

In the expression \( \omega_j \) identifies the \( j_{th} \) path. Rows of the matrix correspond to \( N \) evolution paths derived by simulation; columns correspond to the \( M \) elements of selected basis functions set.

It is useful to define the vector \( \Lambda_i \) whose elements are the \( M \) unknown coefficients at \( i_{th} \) time node:

A.27 \( \Lambda_i(k) = (\alpha_k)_i \)

The algorithm has the goal of finding \( \Lambda_i \) that minimises the 2-norm \( \| A_i \cdot \Lambda_i - Y_i \|_2 \) that by definition is:
In the expression $Y_i$ is a column vector with $N$ rows, determined by discounting the option price on the $i_{th}$ path from $t_{i+1}$ to $t_i$. It is now necessary to introduce the singular value decomposition of $A_i$ matrix:

$$A_i = U \cdot \Sigma \cdot V^T$$

$U$ is an $N \times N$ orthogonal matrix, $V$ is an $M \times M$ orthogonal matrix and $\Sigma$ is an $N \times M$ diagonal matrix, having the singular values of $A_i$ on its diagonal. For the known properties of singular value decomposition, minimisation of previously defined 2-norm is obtained when $\Lambda_i$ is defined as follows\(^{19}:

$$\Lambda_i = V \cdot \Sigma^{-1} \cdot U^T \cdot Y_i$$

It is important to note that the algorithm can be used also if there are more state variables, as it often happens with financial options. In this case the approximating expression will be more complex than in Eq. A.24. For instance, with two state variables, indicated as $X_1$ and $X_2$, a possible definition is the following:

$$F(\omega, t_i) \approx \sum_{k=0}^{M-1} \left[ \alpha_k \cdot L_k(X_1) + \alpha_{k+M} \cdot L_k(X_2) \right] + \sum_{p=1}^{2} \sum_{q=1}^{2} \alpha_{2M+p+q-3} \cdot L_p(X_1) \cdot L_q(X_2)$$

\(^{19}\) Exact inversion of $\Sigma$ is not possible, not being a square matrix. In the formula the pseudo-inversion operator is used instead.
In this case the basis functions set size M will be:

A.32 \[ M = 2 \cdot M' + 4 \]

It is interesting to note that a very large set is not needed. In their paper Longstaff and Schwartz present an example of an option pricing problem involving two state variables. Their set includes a constant, the first two Laguerre polynomials evaluated at the former variable, the first two Laguerre polynomials evaluated at the latter one and their cross products up to the third order terms, for a total of eight basis functions.

For practical uses it is recommendable to normalise the arguments of basis functions to a reference value for each state variable rather to use them directly, as in Eq. A.31 definition. For instance:

\[
\begin{align*}
F(\omega, t) & \approx \sum_{k=0}^{M-1} \left[ \alpha_k \cdot L_k \left( \frac{X_1}{X_{1,0}} \right) + \alpha_{k+M} \cdot L_k \left( \frac{X_2}{X_{2,0}} \right) \right] + \\
& + \sum_{p=1}^{2} \sum_{q=1}^{2} \alpha_{2M' + 2p + q - 3} \cdot L_p \left( \frac{X_1}{X_{1,0}} \right) \cdot L_q \left( \frac{X_2}{X_{2,0}} \right)
\end{align*}
\]

In the expression \(X_{1,0}\) and \(X_{2,0}\) are two normalization values of the state variables.
References


[26] *Market Assessment for Malaria Vaccines*, Boston Consulting Group, 2005


[28] J. Esparza et al., *Estimation of “needs” and “probable uptake” for HIV/AIDS preventive vaccines based on possible policies and likely acceptance*, WHO/UNAIDS/IAVI, 2002


Acronyms

AIDS Acquired Immune Deficiency Syndrome
BCG Bacillus Calmette-Guérin
BVGH BIO Ventures for Global Health
CHOICE CHOosing Interventions that are Cost Effective
DALY Disability-adjusted life years
DTP3 Diphtheria-Tetanus-Pertussis
EFPIA European Federation of Pharmaceutical Industries and Associations
EPI Expanded Program on Immunization
GAVI Global Alliance for Vaccines and Immunization
GDB Global Disease Burden
HAART Highly Active Antiretroviral combination Therapies
HIF Health Impact Fund
HIV Human Immunodeficiency Virus
IAVI International AIDS Vaccine Initiative
IPIF International Pharmaceutical Innovation Fund
NCE New Chemical Entity
NPV Net Present Value
OTA Office of Technology Advancement
PHRMA Pharmaceutical Research and Manufacturers of America
QALY Quality-adjusted life years
STD Sexually Transmissible Disease
TRIPS Trade-Related Aspects of Intellectual Property Rights
UN United Nations
UNAIDS United Nations AIDS
USD United States Dollar
WHO World Health Organisation
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