Working Paper No. 2013/07

Pharmaceutical Portfolio Management: Global Disease Burden and Corporate Performance Metrics

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February 2013

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ACKNOWLEDGMENTS

This study has been supported by Janssen, a Johnson & Johnson company. The authors were free in study design, collection, analysis, and interpretation of data, as well as writing and submitting the article for publication. The views expressed in this publication are those of the authors. Publication does not imply endorsement by the School or the sponsors, of any of the views expressed.
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<td>AMC</td>
<td>Advance Market Commitment</td>
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<td>CAPM</td>
<td>Capital Asset Pricing Model</td>
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<tr>
<td>DALE</td>
<td>Disability-Adjusted Life Expectancy</td>
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<td>DALY</td>
<td>Disability-Adjusted Life Years</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>GDP</td>
<td>Gross Domestic Product</td>
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<td>HealY</td>
<td>Healthy Life Year</td>
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<td>HDI</td>
<td>Human Development Index</td>
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<td>Quality-Adjusted Life Years</td>
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<td>WHO</td>
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ABSTRACT

BACKGROUND
Consistent with good corporate citizenship and the role of multinational pharmaceutical corporations in producing social goods, there is a need to clarify the concept of global burden of disease (GBD) and create performance metrics that measure a firm’s contribution to ‘saving lives’ through its current portfolio as well as identify future opportunities for enhanced product/service offering.

OBJECTIVE
The purpose is to develop besides a conceptual framework an analytic decision-making tool to assess and enhance a firm’s contribution to reducing the burden of disease, and to propose pathways on how this can be accomplished by optimizing the social and business returns on investment thereby maximizing the outcome for all stakeholders (i.e. patient, government, payer and firm).

METHODOLOGY
Product development and financial parameters are connected in an analytic decision model in combination with disease burden metrics. Through event study methodology, we subsequently explore solutions to a number of market, technology, and system issues leading to a disparity between socially and privately appropriable benefits. This is examined through a series of case studies.

The GBD-based theoretical framework provides a general overview and at the same time an assessment of the social return on investment (SRI) as well as the contribution made by any specific compound or project that together constitute the company’s portfolio – now and in the future. The social outcome (SRI) is commonly expressed as Disability Adjusted Life Years (DALYs) averted and the preferred indicator of how successful the burden of disease has been reduced. Simultaneously, the business return on investment (BRI) is computed, capturing the R&D costs and risks in a modular fashion, allowing executives to calculate the profitability index for each product or project.

CONCLUSION
This paper contributes to the burgeoning literature on medical innovation and the ambition to broaden access to medicines. The relationship between a firm’s product outcomes and its corporate social responsibility is examined in the context of a globalizing world still dominated by different national economies and healthcare needs. To better accommodate these needs a holistic framework is required that captures the demands of those living in high, middle and low-income countries.

We believe the suggested framework is able to accomplish this goal and essentially provides a more holistic product portfolio management tool that links the social and business returns of pharmaceutical innovation into a coherent analytic and decision framework, while also providing a dynamic view on how the results obtained along each of the core axes can be improved or optimized.
INTRODUCTION

Medicines prevent and treat diseases, enabling people to live longer, healthier and more productive lives, and consequently contribute significantly to social and economic advances. Innovation-driven pharmaceutical and life sciences companies are the prime innovators of drugs, vaccines and diagnostics.

Consistent with good corporate citizenship and the role of pharmaceutical corporations in producing social goods, there is a need to clarify the concept of global burden of disease (GBD) and create corporate performance metrics that measure a pharmaceutical firm’s contribution to ‘saving lives’ through its current portfolio as well as identify future opportunities for enhanced product/service offering.

The purpose of the study is to develop a conceptual framework and associated decision-making tool to assess and enhance a company’s contribution to reducing the burden of disease, and to propose pathways on how this can be accomplished by optimizing the social and business returns on investment thereby maximizing the outcome for all stakeholders (i.e. patient, government, payer and firm). We argue that the proposed framework is able to accomplish this goal and essentially provides a product portfolio management tool that links the anticipated social and business returns on investment into a coherent analytic and decision framework, while providing a dynamic view on how the results obtained along each of the core axes can be improved or optimized.

Product development and financial parameters are connected in a decision analytic model in combination with disease burden metrics. Through event study methodology, we subsequently explore solutions to a series of market, technology and health system-related issues that lead to a disparity between socially and privately appropriable benefits. Through the case studies, a number of propositions can be tested and strategic implications derived that can be applied to the wider portfolio.
FRAMEWORK: LINKING SOCIAL AND BUSINESS RETURNS

DYNAMIC VIEWPOINT

The emphasis of this study initially lies on understanding the notion of ‘global burden of disease’ before exploring pathways on how this concept can contribute to identifying, measuring and valuing corporate contributions and achievements in global market access and product portfolio management.

The first ever global assessment of disease and injury, the Global Burden of Disease (GBD) Study, was carried out by C.J.L. Murray and A.D. Lopez, in collaboration with a global network of over 100 scientists expert in various diseases and injuries (Murray and Lopez, 1997). The results of the original Global Burden of Disease Study and, particularly, as of the 2000-2002 update provide a conceptual and methodological framework to quantify and compare the health of populations using a summary measure of both mortality and disability: the disability-adjusted-life-years (DALY). The study was undertaken for the World Bank’s pioneering Report on Investing in Health (World Bank, 1993). In recent years, the World Health Organization (WHO) published consecutive revisions and updates, including trend analysis and projections from the year 2004 onwards, over 2015 up to 2030 (WHO, 2008).

The DALY concept and metrics allow the disease burden from premature mortality and that from the non-fatal consequences of over 100 diseases and injuries to be quantified simultaneously. Lopez and Mathers (2006) stated that any health planning and decision making process ought to be based on a thorough understanding of the health needs of the entire population. To that end, a large volume of information on population health was analysed and synthesized to produce comprehensive information on the causes of loss of health – globally, regionally, and particularly for the low-and middle-income countries where there are considerable limitations of data availability.

Despite its utility in health planning, we believe that the DALY concept should be broadened if used by corporations to assess the unmet medical need and market opportunities that they may consider to invest in. In an attempt to rank product-related opportunities we have explored a holistic approach by introducing a composite index that combines the clinical burden of disease ranking (DALY index) with economic parameters such as the ability-to-pay (prosperity index), and the capacity of countries to finance health care (health systems index). While the clinical parameter remains the bedrock of the analysis it is important to consider access barriers as well. If people cannot afford the medicine or the health system is underdeveloped this would hamper the access to medicines and as a result limit the ‘capacity to benefit’, that is the capacity for a patient in a specific economic and health care context to benefit from pharmaceutical innovation. Consequently, the DALY metric measuring disease burden from a clinical perspective should be combined with the above parameters into a composite index i.e. the Disease Burden Composite Index (DBCI). This is illustrated in figure 1.

INSERT FIGURE 1 HERE
To assess the market potential and the anticipated technical ability of the company to successfully address the unmet need, the Disease Burden Composite Index (DBCI) is plotted on the Y-axis against the product’s comparative profile and intrinsic performance (X-axis). This capability analysis is illustrated on the left hand side of figure 2. The result is a SWOT analysis that summarizes the unmet market need, and in turn the market opportunity this represents to innovators. The DBCI component (on the Y-axis) is balanced against the competitive position the company’s technology is likely to occupy (on the X-axis). Thus, the latter is a reflection of the product’s performance (X-axis) which can be captured either as the incremental quality adjusted life years (QALY) that can be obtained with this product, or conceivably can be expressed as the product’s incremental cost-effectiveness ratio (ICER). Although in both cases the improvement in health is considered to be the single most important benefit of medicines, and QALYs generally recognized to be a practical tool for measuring this, its use reportedly is not without challenges in measuring and valuing health states. Debate is going on how to capture and reward the value of medical innovation (Towse, 2012).

Notwithstanding the utility of the above market potential assessment, measuring the size of the total disease burden may be insufficient, even when the clinical, economic and health system aspects are included. Identifying the size of the problem does not tell the whole story if the firm wants to gain insight and ultimately decide on which disease areas to focus on, and this based on its product’s contribution to make an impact and thus reduce the burden of disease while simultaneously earning a return on the investment. Initially, insight can be gained by plotting the ‘problem’ (burden of disease) versus possible ‘solutions’ (existing or improved medicines). However, we believe it is it useful, if not necessary, to add a third dimension to the managerial dashboard, and therefore suggest including the factor ‘return-on-investment’ at least for those diseases and the associated pharmaceutical compounds that the company may decide to focus on eventually. Furthermore, in order to complete the whole picture, the DALYs averted or lost are to be considered instead of the total number of DALYs. This requires calculating the impact of a specific product on reducing the total burden. Accordingly, the analysis becomes more dynamic in nature.

Succeeding the above market potential analysis we recommend to also make a second analysis aimed at explicitly capturing the value proposition of any existing or envisioned future compound. The recommended method computes the social return on investment (SRI) expressed as Disability Adjusted Life Years (DALYs) averted which in that capacity functions as the preferred indicator of how successful the burden of disease can be impacted by using a particular medication. The social index score is plotted along the Y-axis of figure 2. In addition, the business return on investment (BRI) is being computed, capturing the R&D costs and risks in a modular fashion. The outcome allows executives to calculate the profitability index for each product or project. Arguably products that achieve a comparatively high(er) score along the two core dimensions are highly important. Products that score high(er) in one particular dimension deserve great attention as well because they are essential in building a balanced product portfolio, as will be explained in the next sections. The product positions are graphically illustrated in figure 2 now reduced to its core values: SRI and BRI.

**INSERT FIGURE 2 HERE**
The following section clarifies how to compute the social (SRI) and business (BRI) returns on investment, respectively. The input and output variables of the integrated model are summarized in figures 3 and 4.

**THE SOCIAL RETURN**

The SRI indicator aims to quantify and subsequently rank the number of DALYs averted or lost due to the adoption and use of a particular health technology intervention (e.g. drug, vaccine and/or diagnostic). Our principal interest is in finding out how this may serve a company in detecting opportunities and align its performance with external needs. If highly successful, projects would generate both social and business returns. Practical examples can be found in the case studies (see next section).

In practice, the social return index (SRI) uses the DALY metric as the foundation. The DALY metric functions as a *health-gap measure* by extending the concept of the potential years of life lost because of premature death and include equivalent years of ‘healthy’ life lost by virtue of being in a state of disability or poor health. In other words, the DALY combines life lost because of premature death (YLL) and years of life lived with disabilities (YLD) into a combined indicator, allowing an assessment of the total loss of health from different causes. In contrast with the QALY concept, the DALY measures health gaps as opposed to health expectancies. One lost DALY can be thought of as one lost year of ‘healthy’ life, and the total number of DALYS averted as a measurement of the gain between the current ill health of a population and the ideal situation where everyone lives up to the age of the standard life expectancy, and in perfect health. Based on life tables, the standard life expectancy at birth is set at 80 years for men and 82.5 for women (Murray, 1994).

The YLL factor is calculated from the number of deaths at each age multiplied by the standard life expectancy for the age at which death occurs. To estimate YLD for a particular cause in a particular time period, the number of incident cases in that period is multiplied by the mean duration of the disease, on a scale from 0 (perfect health) to 1 (dead). The weights used in the 2000-2002 GBD report and updates thereafter are listed in detail elsewhere (Mathers at al., 2006, WHO report). Additionally, 3% time discounting and non-uniform age-weights, which give less weight to years lived at young and older ages, are used in calculating standard DALY. This is derived from the productivity concept of the human capital method. However, these filters can be removed and reporting is often done with and without age-weights. This does not fundamentally change the ranking.

**THE BUSINESS RETURN**

Project investments and the related risk management decisions are fundamentally important to the development and availability of innovative products that enhance health outcomes and the quality of life. Previous studies consistently found that the anticipated cash flow coming from future sales adjusted for costs made during and after product development is an important
predictor of the ratio of pharmaceutical firms’ R&D expenditures to sales (Grabowski (1968), and Grabowski and Vernon (2000).

In our model, the business return-on-investment (BRI) functions as a performance measure that summarizes the efficiency of the investment. The net present value of future sales is compared to the development and marketing costs, and this is being calculated by using a discount rate that reflects the so-called ‘cost of capital’. This opportunity cost of capital actually is a risk premium used by virtually all private-sector firms as the financial threshold that must be overcome before investing in a risk-bearing activity. Corporate finance theory assumes that firms will pursue all projects for which the expected net cash flows are positive after being adjusted for the opportunity cost of capital (that is, a possible investment in another project of similar risk). Because of the long development cycles and the statistically low scientific success rates for individual projects, the effects of the cost of capital on project investment decisions can be particularly large for the pharmaceutical, biotechnology and medical device sectors. Because of its huge impact on the financial simulation outcome and the resulting management decision to invest or not (i.e. go, no-go, or abort the project), it is important to define the right level of risk premium for pharmaceutical projects.

In a series of empirical investigations, Myers and Shyam-Sunder (1995) at MIT estimated the relative riskiness of 17 major pharmaceutical firms to compute the corresponding pharmaceutical industry’s cost-of-capital values for 1980, 1985, and 1990. Using the Capital Asset Pricing Method (CAPM model), Myers and Howe performed a similar analysis for 1994 (and confirmed the earlier results in 1997). The cost-of-capital estimates were relatively stable over the entire period 1980 to 1994. The estimated cost-of-capital values for pharmaceuticals were found to be 14% (nominal value) and 11% (real value) after adjustment for inflation. However, the authors also pointed out that the associated risk and therefore the associated cost of capital of an individual pharmaceutical R&D project also depends on the stage of the project and on the amount and time of follow-on investments required to arrive at the point of commercial success. Therefore, the technical development phase and commercial phase can be considered distinct stages with different risk factors.

In our model and in line with traditional valuation methods to calculate investment returns by using the net present value (NPV) of cash flows over the entire length of the project, we were inclined to use a single cost-of-capital-based ‘discount rate’ throughout development and commercial launch, that is, throughout the innovation’s entire lifecycle from cradle to grave. However, recent literature warns against using too high a ‘hurdle rate’ (McKinsey, 2012) which risks undervaluing future sales, by reducing the project’s NPV value. This may unnecessarily and prematurely curtail the development of compounds that in essence are worth developing if a less harsh method were to be used in evaluating the potential these compounds may have. Consistent with Myers and Shyam-Sunder’s (1995) “risk-return staircase” theory explained above, we have used two different values for the cost-of-capital – 11% for the development and 8% for the commercialization phase. Although these values can be easily modified in the model, we recommend that instead of sensitivity analysis one method is being used consistently across the portfolio.
Finally, Ross et al. (2010) argue that besides the above NPV method another decision method should be used to evaluate investment projects; called the *profitability index* (PI). It is the *ratio* of the present value of future cash flows after initial investment divided by the amount of the initial investment in the project. By definition, the PI index should be higher than 1 for a project to be profitable.
CASE STUDIES: APPLYING THE CONCEPTUAL FRAMEWORK

FIRST PROPOSITION

“Lack of market demand and financial return on investment weakens the development of drugs, vaccines and diagnostics for third world diseases despite their huge medical need”

<table>
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<th>Case study:</th>
<th>Malaria Vaccine</th>
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<tr>
<td>Proposed solution:</td>
<td>Push/Pull Funding &amp; Incentive Mechanisms to Stimulate R&amp;D</td>
</tr>
<tr>
<td>Applications:</td>
<td>Malaria, Tuberculosis, Dengue, Trypanosomiasis, etc.</td>
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Acemoglu and Linn (2004) published one of the few papers that have estimated a direct causal link between expected market size and innovation in the pharmaceutical and life sciences industries. They found that biomedical innovation is fairly responsive to the expected market size. Other papers in this strand of management literature have used variation in market size induced by discrete policy changes to estimate the responsiveness of innovation (Blume-Kohout and Sood, 2009).

Market demand and market need are not necessarily the same. This is clearly illustrated when dealing with tropical and other poverty-related diseases where the SRI index is likely to be very high but the BRI comparatively low, because of the limited ability to pay. For ‘neglected’ diseases which are mostly infectious diseases that are prevalent predominantly, or sometimes only, in the world’s poorest countries (e.g. malaria, tuberculosis, dengue, etc.), most developing countries’ ability to pay by themselves (without external help) is insufficient, and therefore the market value of the related compounds critically low to stimulate private-sector R&D. By means of the case study concerning development of (future) malaria vaccines, we will review proposals to incentivize R&D leading to medicines for neglected diseases; including “push” mechanisms that subsidize research and “pull” mechanisms that reward research output - e.g. advanced market commitments (AMC).

Advance Market Commitments (AMCs) and Priority Review Vouchers (PRV) are innovative ‘pull’ subsidies that have been created recently and are being applied in a few instances. They have been designed to stimulate work in neglected disease areas with an often high medical need but with poor commercial returns. The AMC concept is a simple one. If a company develops a new product, and the world’s poorest countries demand it, thus the AMC uses funds from rich nations to buy the product at an initial price that covers the company’s investments and risks. The company is then obligated to provide the product to poorer countries at much lower, pre-established prices. Thus, the AMC provides a market where previously there was none, encourages investment in targeted research and development, and rewards specific outputs - in this case, doses of a life-saving drug or vaccine.

The priority review voucher (PRV) program, currently administered by the US Food and Drug Administration (FDA), was passed into United States law in 2007 as a ‘pull mechanism’ to help promote R&D for medicines targeting neglected tropical diseases (FDA, 2012). Under this law,
companies that receive FDA approval for a novel drug or vaccine targeting one of 16 tropical diseases are awarded a transferable voucher. This voucher can be sold to a second organization or can be redeemed to grant the bearer a priority six month review for another medicine of their choosing (FDA, 2008). As average standard review periods can range between 10–16 months, the voucher could potentially allow products to reach the market up to eight months earlier. For a company with an anticipated top selling medicine that is expected to generate a peak sales value close to $3 billion, for example, the innovators of the mechanism predicted that the accelerated approval could be worth over $300 million. However, the impact in practice of the PRV incentive in developing new medicines for neglected tropical diseases has been questioned, in part due to uncertainty around the value of the voucher among R&D-based pharmaceutical and biotechnology companies (Kesselheim, 2008; Gingery, 2010).

By means of the case study on malaria vaccine, we intend to explore the impact that these incentive mechanisms may have on stimulating pharmaceutical innovation. We argue that push and pull incentives are complements and would like to determine the extent to which policies that increase market size are likely to improve the effectiveness of supply-side strategies by reducing the cost of R&D. The BRI-framework that we propose allows us to calculate the minimum size of funding required. At the same time, we argue that a combination of incentives is needed to address this grand challenge.

**SECOND PROPOSITION**

<table>
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<tr>
<th>“Late detection and under-diagnosis of important illnesses that are causing sequelae that predominantly occur later in life result in diminished social as well as business returns”</th>
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<tr>
<td><strong>Case study:</strong></td>
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<td><strong>Proposed solution:</strong></td>
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<td><strong>Applications:</strong></td>
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</table>

The impact of the HCV epidemic, which is already substantial, will manifest itself for decades to come. HCV has mainly been transmitted via blood transfusions prior to the availability of HCV screening tests in 1992, and hence an enormous swath of the world’s population has been left with chronic HCV infection. The actual course of the epidemic is uncertain and will be influenced by a variety of factors, including the creation and implementation of large-scale prevention and treatment efforts. We will show how attention to preventative health care programs through periodical monitoring of healthy patients contributes significantly to reducing patients’ DALY’s and improve patients’ QALY’s.

In the case of hepatitis C viral infection, the key issue to be addressed is the fact that most people that already are infected are initially not aware of the infection because it remains asymptomatic until the stage of cirrhosis or liver cancer. The quest for better care therefore revolves around attempts to improve the diagnosis of citizens and patients before they become severely ill. The phenomenon is not unique and can be witnessed in an increasing number of therapeutic areas like, for example, diabetes, cancer, etc. The proposed solution hinges on the ‘early detection’ and the
‘pre-emptive use’ of therapy that is embedded in disease management programs promoting population-wide screening.

Starting such disease control (or eradication) programs would be timely. Treatments for chronic hepatitis C are evolving at such a rapid pace that in 5 years, interferon-free, oral, direct-acting antiviral regimens may achieve close to 90% cure rates across viral genotypes and regardless of IL-28B allele status. What is currently lacking in this optimistic perspective is a national “find-and-treat” policy aimed at achieving maximum identification of HCV carriers and providing new-generation therapies to a large proportion of those identified cases. Public health experts have stated that in today’s new context the goal to prevent fibrosis progression and cancer evolution in patients with HCV infection is achievable. The individual and societal benefits of such a strategy would be substantial and the costs are in step with other well-established public health measures. (CDC, 2012)

Generally linking patients to care and treatment is a critical component of a strategy to reducing the burden of disease. However, as traditional pegylated interferon–ribavirin therapy has considerable adverse effects and less than 50% sustained efficacy, treatment decisions have been highly variable. Future therapies will overcome this obstacle. Nevertheless, the challenge is to integrate testing to improve health outcomes. Estimates suggest that currently only 10% to 20% of patients known to be infected with HCV accept therapy and complete a full therapeutic course (CDC, 2012). The impact of increasing the number of individuals tested as well as increasing the number of those patients identified and receiving treatment can be calculated with the DALY-based social return model.

**THIRD PROPOSITION**

<table>
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<th>Rare diseases affecting a small percentage of the population rank low in disease burden studies despite their debilitating effect on individuals and require specific policy intervention</th>
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<tr>
<td><strong>Case study:</strong></td>
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<tr>
<td><strong>Proposed solution:</strong></td>
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<tr>
<td><strong>Applications:</strong></td>
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</tbody>
</table>

Similar to what has been proven in the previous case studies; the GBD-based model can be used to calculate the social return on investment (SRI) and the business return on investment (BRI) for ‘orphan drugs’ that are addressing ‘rare diseases’. The challenge is different here due to the low frequency of these diseases making the technical, market and financial challenges higher than in most of the other disease categories. Therefore, concerted efforts are needed between the key stakeholders.

A rare disease, also referred to as an orphan disease, is any disease that affects a small percentage of the population. There is no single, widely accepted definition for rare diseases, however. In the United States, the Rare Disease Act of 2002 defines rare disease strictly according to prevalence, specifically “any disease or condition that affects less than 200,000 persons in the United States” (Illingworth et al., 2004) or about 1 in 1,500 people. In Japan, the legal definition of a rare disease is one that affects fewer than 50,000 patients in Japan, or about 1 in 2,500 people. A link between
the incidence of illness and policy is made by the European Commission on Public Health defining rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them."

The term low prevalence is later defined as generally meaning fewer than 1 in 2,000 people. Diseases that are statistically rare, but not also life-threatening, chronically debilitating, or inadequately treated, are excluded from this definition.

Rare diseases usually are genetic (Aymé et al., 2007), hence chronic. It is estimated that at least 80% of them have identified genetic origins. Other rare diseases are the result of infections and allergies or due to degenerative and proliferative causes. Rare diseases can vary in prevalence between populations, so a disease that is rare in some populations may be common in others. An example is cystic fibrosis, a genetic disease: it is rare in most parts of Asia but relatively common in Europe and in populations of European descent. Symptoms of some rare diseases may appear at birth or in childhood, whereas others only appear once adulthood is reached. All forms of cancer in children are considered rare, because so few children develop cancer, but the same cancer in adults may be more common.

Because of these limitations in population size, drug development to tackle orphan diseases poses special challenges. The hurdles that must be overcome vary in nature and are fundamentally linked to technical development and market access issues. Due to the low incidence, it is hard to find enough patients for clinical studies and data from various sites are combined. Moreover, clinical testing does not end once a drug has been approved for marketing. Although regulatory bodies do not have the formal authority to require clinical testing after a drug is approved, it may hold up drug approval unless the drug company ‘voluntarily’ agrees to conduct so-called phase IV clinical trials. Although some of these phase IV obligations involve placebo-controlled trials, many require long-term and large-scale observational studies. The purpose of these studies is to identify side effects that are serious but so rare that even phase 3 trials are not sufficiently large to detect them.

From a capital budgeting perspective, it is hard to justify investment into the development of orphan drugs since some conditions occur so infrequently that the cost of developing and bringing such products to the market would not be recovered by the expected sales. This warrants government intervention and some jurisdictions have put forward incentives to stimulate the development of drugs for rare diseases. Following the successful Orphan Drug Act in the USA, the European Union introduced its Regulation of Orphan Medicinal Products in 2000. However, to be designated orphan drug status does not automatically mean that a drug will be authorized for marketing. During the past ten years, a number of 1049 orphan designations have been provided in the United States and 112 products have obtained marketing authorization. In the European Union, 615 products have orphan status, of which, 59 were authorized for marketing. Due to the relatively low number of orphan drugs approved there has been criticism that the development has been too slow (Heemstra, 2010).

The above observations give strong impetus to the question of what determines successful development and marketing authorization of an orphan drug. In other words, what makes an orphan designation result in an authorization? What are the effects of various public policies to

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1 http://ec.europa.eu/health-eu/health_problems/rare_diseases/index_en.htm
stimulate innovation in this field? And, what are the predictors of successfully attaining market access?
STUDY OUTCOME: PRODUCT PORTFOLIO MANAGEMENT

The case studies have been randomly selected and reflect real world situations. They illustrate the process of strategic mapping alongside the two core axes of social and business return, SRI and BRI, respectively. Each key learning has wider repercussions and together these cases illustrate the challenges faced by innovation-driven companies, and how several issues can be overcome through collaboration between the various stakeholders representing business, government and society.

MALARIA VACCINE

Malaria infects 300-500 million people per year the majority of which reside in poor countries, representing 32.3 million DALYs. An effective vaccine against malaria has long been envisaged as a valuable addition to the available tools for malaria control. There are as yet no licensed malaria vaccines. According to the WHO malaria report (WHO, 2011), a single candidate vaccine is currently being assessed in phase III clinical trials, and approximately 20 other projects are in phase I or phase II clinical trials.

The population target group that is envisaged for malaria vaccines is African infants resident in malaria endemic countries, with vaccination administered at 6–14 weeks of age, together with other vaccines administered routinely to infants. The preliminary results from the phase III trial of the GSK ‘first generation’ vaccine found an efficacy of 35% with short-lived duration, and the full trial results are expected to become available in late 2014. In the longer term, the objective is to work towards the 2025 goal of developing and testing a vaccine with at least 80% efficacy against clinical malaria.

To bridge the R&D investment gap, the industrialized world’s ‘donor’ countries, NGO’s and foundations could spur innovation in two important ways. They can pursue a dual strategy of providing important direct and indirect subsidies -- known as push mechanisms -- to organizations that develop new products for global health needs, and also provide financing measures like the Advance Market Commitment (AMC) and Priority Review Voucher (PRV) - known as pull mechanisms. The latter mechanisms use market forces to encourage research and development similar to what is done for other innovative products in other therapeutic areas, in order to spur private-sector innovation by creating a viable market for products where the consumer buying power is low.

The cost-effectiveness of child vaccination in malaria endemic countries and the likely impact of prototype vaccines on reducing the burden of disease have been described in the literature (Penny et al, 2008). These studies suggest that at moderate to low vaccine prices, a first generation, pre-erythrocytic vaccine providing partial protection, and delivered via the existing UNICEF EPI program, may be a cost-effective intervention in countries where malaria falciparum is endemic. Unsurprisingly an 80% efficacious vaccine would even be more beneficial and widely accepted. We have used these data to assess the external funding needed to stimulate product development. Under the scenario of no-gain/no-loss, that is, with an expected NPV equal to zero, the funds needed would amount to $5-7 billion to attract three competitors, and guarantee R&D and supply security over a twenty year period. Since the challenge is enormous, further research is needed on
how to combine various push and pull incentive mechanisms to encourage research on tropical diseases.

**HEPATITIS C DRUG**

As mentioned earlier, campaigns targeted at individuals to become tested have thus far not been sufficiently effective. Recommendations that physicians routinely ask questions about HCV risk have fallen victim to a number of logistical and sensitive issues. To effectively reduce the burden of the HCV epidemic, public health experts advocate for a new approach to be taken that would shift the focus from the ad-hoc individual approach to a concerted, wider societal line of attack (CDC, 2012).

To effectively tackle the under-diagnosis issue, the Centers for Disease Control and Prevention (CDC) in the United States have proposed a clever strategy that targets the highest-risk birth cohorts. CDC is recommending that everyone born during 1945 through 1965, also known as *baby boomers* get a blood test for Hepatitis C. The CDC estimates that although persons in this subpopulation comprise an estimated 27% of the population, they account for approximately three fourths of all HCV infections in the US, 73% of HCV-associated mortality, and are at greatest risk for hepatocellular carcinoma and other HCV-related liver disease. With the advent of new therapies that can halt disease progression and provide a virologic cure (i.e., sustained viral clearance following completion of treatment) in most persons, targeted testing and linkage to care for infected persons in this birth cohort is expected to reduce HCV-related morbidity and mortality. Familiarity with the targeted population and the term used to describe it is expected to facilitate adoption.

Figure 5 summarizes the social and business returns for a next generation compound based on its sales forecast mapped against standard assumptions about product development costs, resulting in a risk-adjusted profitability index (X-axis) versus averted DALYs (Y-axis). As such, improved treatments for hepatitis C follow their now-destined progression, the most burning question will not be whether to treat, but rather how to identify the many chronic HCV carriers who are unaware of their infection and are at risk of cirrhosis, end-stage liver disease, or hepatocellular carcinoma. With that objective in mind, the likely impact of a test-and-treat strategy can be simulated with our model. DALYs averted are likely to increase although not in a linear fashion because of health-system variables. Simultaneously, the business return may improve although this may be partially off-set by the increased marketing and distribution costs. To succeed, the company will have to find public-sector partners to roll out these programs in the various parts of the world.

**RARE DISEASE DRUG**

It is generally recognized that without accompanying public incentives it is unlikely that the development and marketing of rare disease medicines would generate sufficient return to justify private-sector investment. The issue is not the intrinsic inability-to-pay of patients which is the case for tropical neglected diseases (as described in the Malaria study). Since the market size for *orphan drugs* with a limited application scope would, by definition, be small and thus largely unprofitable,
government intervention is necessary to motivate manufacturers to address the need for such drugs.

Advocacy efforts driven by patients’ organizations to make rare diseases a health priority have led to regulatory and economic incentives for industry to develop drugs for these diseases, known as orphan drugs. These incentives, enacted in regulations first introduced in the United States and later in Japan, Europe and elsewhere, have resulted in substantial improvements in the treatment for patients with a range of rare diseases. Such interventions by government on behalf of orphan drug development in principle can take a variety of forms, including: tax incentives, enhanced patent protection and marketing rights, clinical research financial subsidization, or creating a government-run enterprise to engage in research and development. While the latter would not resolve the issue of negative returns on investment, a combination of incentives has been introduced.

Lichtenberg and Waldfogel (2008) analyzed the effects of the US Orphan Drug Act (ODA) on pharmaceutical innovation and found that it significantly increased new drug introductions. Yin (2008) also found that the ODA had a significant impact on development of drugs for rare diseases. The seven-year market exclusivity period in the ODA was characterized as the most sought-after incentive. If a market competitor wishes to introduce a drug for the same indication, the onus is on the competitor to prove that their drug is therapeutically superior (e.g. increased efficacy, less toxicity, etc.) when compared to the present drug indicated for the rare disease of interest. While this incentive creates an attractive monopolistic market for companies interested in developing a product for any given rare disease, in practice a gap remains between the number of products that have received orphan status and the number of products that are actually launched to benefit patients.

Studies found that besides market exclusivity other measures could accelerate market access Heemstra (2010). An important predictor for successful launch is the level of experience of a company in obtaining market authorization for orphan drugs. Pharmaceutical companies that have brought an orphan drug to the market increase their odds of obtaining market authorization for consecutive products more than 17-fold. This result seems straightforward; however, a majority of all orphan designations is being developed by small and medium sized enterprises with limited prior experience in this domain. Thus authorities can address this issue by offering protocol assistance and scientific advice. In addition, patient groups are able and willing to be mobilized in the set-up of clinical trials. Another important aspect concerns improved access to information for both patients and health professionals; considered indispensable for good quality care (Eurordis, 2012).

Figure 5 illustrates the likely position occupied on the product portfolio map by rare disease drugs. Whereas the SRI score inevitably will be low at the aggregate level for reasons explained above; the individual patient score will be high given the severity of this type of diseases. By itself this may not suffice to recoup investments made. A possible solution is to dramatically increase the price of these drugs. Even though such diseases predominantly occur in high-income countries, this would raise issues of affordability. Policy actions like the orphan drug act have a beneficial effect. The cost of development is partially off-set and prices are less high compared to what they otherwise would
be. Such measures are indispensable for firms to actively pursue investment in orphan product R&D.

**INSERT FIGURE 5 HERE**
DISCUSSION: STRATEGIC MANAGEMENT IMPLICATIONS

The objective that we have set out was to demonstrate through a number of case studies the applicability of the GBD-based strategic portfolio framework. As a result, we have demonstrated how to calculate the SRI and BRI index, and how the dynamic mapping of relative product positions provides strategic insight from a ‘static/what is’ perspective (i.e. describing and accepting the current development trajectories and likely commercial forecast scenarios), as well as from a ‘dynamic/what could be’ viewpoint (i.e. illuminating pathways to improve the societal and business returns).

- In the case of malaria, for instance, the key learning in our opinion has been about how the private sector (pharmaceutical and biotech companies) and the public sector (governments) could collaborate and come to an agreement on how to stimulate and accelerate the research and development of, as well as improve the access to, new medicines that would address poverty-related diseases afflicting predominantly developing countries. It is argued that this can best be achieved through partnership and the provision of external funding. In that context, the malaria case can be extended to include about all tropical and poverty-related diseases.

- In the case of hepatitis C, the issue to be addressed to control the disease hinges on successfully implementing programs that would change the fact that nowadays most people infected are initially not aware of the infection and that it remains asymptomatic until the stage of cirrhosis or liver cancer. The proposed solution revolves around the ‘pre-emptive use’ of next generation drugs embedded in disease management programs that promote screening of individuals. The CDC program of screening ‘baby boomers’ is taken as an example of a targeted, mass-screening program in combination with early treatment and the prevention of symptomatic cases.

- In the case of drugs that combat rare diseases, there is legislation that provides a financial incentive together with market exclusivity to companies willing and able to develop orphan drugs. The assignment of orphan status to a disease and to any drugs developed to treat it is a matter of government policy and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics of drug research and product development. Nonetheless, a number of market access issues must be resolved. Even though the framework is able to calculate the social and business impact, the DALY impact inevitably will be lower than for other diseases. This has nothing to do with the DALY metric but with the very low incidence of this type of diseases. This makes sense from a public health perspective (but less of course from an individual viewpoint). Yet, the system handles this well. The BRI is likely to score high, while the SRI may be modest. The BRI is high because society’s willingness to pay is high.

The GBD-framework as presented here was designed for use at headquarters level. However, it can also be used by country operations and regional headquarters. In that case, the worldwide market view is replaced by a local market perspective again aimed at stimulating creative thinking and defining pathways and activities to advance the company’s product strategy, improving its
competitive position, and enhancing market access through a number of programs as demonstrated in the case studies. In the event of using the model locally, the research and development costs should be replaced by sales, marketing and medical affairs costs to arrive at a product-related cash flow that is relevant to local affiliates. A shift in the relative positions occupied by different products on the strategic grid may occur in line with the underlying epidemiology and competitive position. The method is expected to help define regional/country priorities.

An important question is whether the GBD-based portfolio framework can be used universally? In other words, can it be used across therapeutic areas regardless of whether the purpose is treatment, diagnosis or prevention? Having now worked under various circumstances with the ‘Symphony’ tool, we are convinced that it can be used to assess the relative positions of virtually all of the illnesses reported in the WHO GBD report. The calculation is straightforward when using DALYs as the metric. However, the system is laborious in searching the literature for the impact of the technology. There is no easy way out unless future studies offer a precise measure for the DALY or QALY impact of the firm’s products. One could also envisage developing a multi-disease epidemiology model to facilitate assessing the burden of disease, similar to the WHO PopMod model2.

With regard to the selection of DALYs as the preferred metric, there is no doubt in our mind that this is the best and possibly the only way to measure the impact on the burden of disease. Using the disability-adjusted life years metric (DALY) as the primary indicator, adequately summarizes the burden of premature mortality and disability. Other methods that we looked at and that have been debated in the past in literature are less complete, or do not allow comparing results globally in a standardized fashion, and across various therapeutic areas. More research is needed to compare DALYs and QALYs, however. In particular, the conversion between these two metrics warrants further investigation. Further research is already going on to refine and continuously update the DALY disease burden input data. During the writing of this report, the Institute for Health Metrics and Evaluation of the University of Washington in Seattle has published its findings on worldwide trends in disease burden. This update can be seen as a follow up of previous reports published under the auspices of the WHO of which the consolidated data have been used in this study (WHO, 2008).

As a final point, corporations should not feel compelled to score high in all disease areas and on all the indexes proposed. Rather, a trade-off should be pursued between diseases with high SRI and low BRI, and vice versa. The goal should be to build a balanced portfolio meaning that a healthy balance should be achieved at the aggregate level. Given the varying nature of disease burden patterns across nations and population groups, corporations focusing on modern, lifestyle diseases as well as poverty-related diseases are in a position to score high in both the social and business ranking.

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CONCLUSION

The purpose of this project was to develop a conceptual framework and related analytic decision tool to assess a pharmaceutical firm’s contribution to reducing the global burden of disease, and to propose pathways on how this can be accomplished by optimizing the social and business returns on investment, in that way maximizing the outcome for all stakeholders (patient, government, payer and firm).

We believe that the framework developed is able to accomplish this unifying goal and essentially provides a portfolio management tool that links the social and business aspects into a coherent analytic decision framework. It also provides a dynamic view on how the results obtained along each of the core axes can be improved or optimized. So, the model helps building “A Balanced Portfolio”.

The study contributes to the burgeoning literature on innovation and the ambition to broaden access to medicines. The research provides further insight into the relationship between the outcomes that are, or will be, produced by the firm’s products and services and its corporate social responsibility. This is examined in the context of a globalizing world still dominated by different national economies and health care needs. Taking into account all unmet medical needs requires a holistic framework that captures the demands of those living in high, middle and low-income countries.
**Figure 1**

**DBCI COMPOSITE INDEX**
INTEGRATING EPIDEMIOLOGICAL, ECONOMIC & HEALTH SYSTEM INDICATORS

- **Clinical**
  - Disease Burden
  - DALY
  - Disease Burden Index

- **Economic**
  - Affordability
  - GDP
  - Country Prosperity Index

- **Health System**
  - Accessibility
  - Insurance Coverage
  - Health Systems Index

**Dimension**
- DBI
- CPI
- HSI

**Index**
- Disease Burden Composite Index (DBCI)

**Figure 2**

**GLOBAL BURDEN OF DISEASE FRAMEWORK & CORPORATE PERFORMANCE METRICS**

- **"STATIC"**
  - 'MARKET POTENTIAL'
  - ‘THE PROBLEM’
    - Worldwide Burden and Cost of Illness
    - Epidemiology (Incidence & Prevalence)
    - Ability to Benefit (Access & Affordability)

- **"DYNAMIC"**
  - 'VALUE PROPOSITION'
  - SOCIAL IMPACT (SRI)
    - Lives Saved / Quality Added
    - DALYs Averted / QALYs Gained
    - Attributed to Specific Product

- **"THE SOLUTION"**
  - Health Care Policy Decisions
  - Health Technology & Services
  - Drugs, Vaccines & Diagnostics

- **BUSINESS IMPACT (BRI)**
  - Revenue Net Present Value
  - Profitability Ratio and Index
  - Attributed to Specific Product

- FROM A GLOBAL PORTFOLIO MANAGEMENT AND OPTIMIZATION ANALYSIS
GLOBAL BURDEN OF DISEASE FRAMEWORK AND PERFORMANCE METRICS OVERVIEW

GLOBAL BURDEN OF DISEASE

MODEL INPUT

PRODUCT COMPETITIVE PROFILE

MODEL OUTPUT

SOCIAL RETURN ON INVESTMENT

SOLUTION
Rx, Vx and/or Dx

BUSINESS RETURN ON INVESTMENT

FIRST PAY OFF
Lives Saved
Morbidity/Mortality

SECOND PAY OFF
Profitability Index

KEY PARAMETERS OF THE DECISION ANALYTIC MODEL

GLOBAL BURDEN OF DISEASE

MARKET OPPORTUNITY

PHARMA TECHNOLOGY SOLUTION

COMPOSITE INDEX (DBCI)
- Clinical (DALY metric)
- Economic (ATP metric)
- Health Systems (OOP metric)

COMPOSITE INDEX (PCPI)
- Clinical efficacy
- Mode of administration
- Benefit to risk ratio

COMPOSITE INDEX (SRI)
- Reduction of morbidity and mortality (DALY metric)
- Averted deaths

COMPOSITE INDEX (BRI)
- Expected Net Present Value (ENPV)
- Expected Profitability Index (EPI)

DBCI: Disease Burden Composite Index; PCPI: Product Competitive Profile Index; SRI: Social Return Index; BRI: Business Return Index

DALY: Disability-Adjusted Life Years; ATP: Ability to Pay; OOP: Out-of-Pocket Health Expenditure

Rx: Prescription; Vx: Vaccination; Dx: Diagnostics
Figure 5

**STRATEGIC PORTFOLIO MAPPING**

<table>
<thead>
<tr>
<th>PRODUCT IMPACT ON DISEASE BURDEN</th>
<th>PRODUCT SPECIFIC PROFITABILITY INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra High</td>
<td>B+++</td>
</tr>
<tr>
<td>Very High</td>
<td>C++</td>
</tr>
<tr>
<td>High</td>
<td>D+</td>
</tr>
<tr>
<td>Significant</td>
<td>C</td>
</tr>
</tbody>
</table>

**SRI (SOCIETAL RETURN)**
- Days Averted (M)

**BUSINESS RETURN (INDEX)**
- Negative
- Ultra High
- Very High
- High
- Significant

**Note:**
Three Case Studies:
The positions for Malaria vaccine, Hepatitis C drug and Rare Disease drug have been calculated with the GBD-based framework with data obtained from literature.

**Note:**
Hepatitis C cases detected through screening are assumed to increase the coverage rate gradually from 20% to 25% (see Annex 2: US CDC Baby Boomers Screening Program).

**Legend:**
- **MALARIA VACCINE**
  - 1st Generation Excl. Funding
  - 2nd Generation Excl. Funding
- **HEPATITIS C DRUG**
  - Worldwide
  - G7 + Screening
  - G7 Markets
- **RARE DISEASE DRUG**
  - Excl. Legislation
  - Incl. Legislation
- **ORPHAN DRUG LEGISLATION**
  - External Funding

**Product Impact on Disease Burden:**
- Very High
- High
- Significant

**Product Specific Profitability Index:**
- B+++ Ultra High
- C++ Very High
- D+ High
- C Significant
- B High
- A Very High
- Ultra High
- Very High
- High
- Significant

**Note:**
- Malaria vaccine
- Hepatitis C drug
- Rare Disease drug
- Literature

**External Funding:**
- Malaria Vaccine
- Hepatitis C Drug
- Rare Disease Drug

**Internal Funding:**
- Malaria Vaccine
- Hepatitis C Drug
- Rare Disease Drug
REFERENCES


