Personalized Medicine, Bioethics and Social Responsibilities: Re-thinking the Pharmaceutical Industry to Remedy Inequities in Patient Care and International Health

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Abstract: US Senator Barack Obama recently proposed the Genomics and Personalized Medicine Act of 2006, which should it be enacted, would establish a Genomics and Personalized Medicine Interagency Working Group to coordinate personalized medicine efforts, fund genomics research to improve drug safety and establish a US Biobanking Research Initiative similar to efforts deployed in other countries. But what impact could personalized medicine have on the drug development process, the pharmaceutical industry and international health, including that in developing countries? Can personalized medicines support innovation, sustainability and growth in the pharmaceutical industry and also respond to changing world realities, emerging public demands for safer and more efficacious medicines and equitable access to pharmaceuticals? The present paper examines these socio-ethical and science policy questions by first elucidating their intrinsic and often complex interactions with other economic and policy issues (and the often divergent interests of stakeholders). We then present some examples from other industries (e.g., the case of hybrid cars and attendant growth of consumer interest and confidence in high quality sustainable products), with a view to identifying the factors that might contribute to a successful integration of pharmacogenomics and related biomarker technologies in patient care, international health and public policy. In particular, we propose ways to integrate the concept of sustainability into corporate and investor models of pharmaceutical industry development. While the power of pharmacogenomics to serve as a driver for the pharmaceutical industry remains to be evaluated, we submit that biomedical innovation and economic prosperity can co-exist with ethical drug development and the sustainable commercialization of customized drug therapies.

Key Words: Pharmacogenomics, personalized medicine, bioethics, social responsibility, sustainability, international health, economics, inequity, distributive justice, business ethics, World Health Organization, science policy.

“Sustainable development is...development that meets the needs of the present without compromising the ability of further generations to meet their own needs.”


“Our ideals, laws and customs should be based on the proposition that each generation, in turn, becomes the custodian rather than the absolute owner of our resources and each generation has the obligation to pass this inheritance on to the future.”


INTRODUCTION

There has been considerable academic, public and policy debate about the safety and efficacy of drugs, and their impact on remediating important local, national and global health concerns [Bondy, B. and Zill, P. 2004; Kirchheiner, J. et al., 2005; Service, R.F. 2004]. These concerns often relate to the contributions of pharmaceutical research to public health. Specifically, adverse drug reactions (ADRs) rank as the fourth leading cause of death, ahead of pneumonia, diabetes and traffic accidents [Lazarou, J. et al., 1998], and only about half of patients treated with conventional blockbuster drugs adequately respond to pharmacotherapy [Spear, B.B. et al., 2001]. In the context of international health, of the 1233 new drugs marketed between 1975 and 1999, only 13 were approved for treating tropical diseases affecting developing countries, seriously impairing access to necessary health care in these regions [ACHR, 2002]. According to the World Health Organization (WHO), in most low income countries pharmaceuticals are the largest public expenditure on health after personnel costs, and the largest household health-related expenditure [Ozdemir, V. et al., 2006a; WHO, 2007a]. When comparing the 60-80% of health expenditures that patients in low income countries have to cover themselves, with the 30-35% of health expenditures covered by individuals in high income countries, the extent of disparities in access to health care become striking.

Personalized medicine may offer some remedies to these challenging public health concerns. In this regard, the pharmaceutical industry has made important contributions, in particular to support efforts to utilize new health technologies, such as pharmacogenomics, directed at identifying novel drug targets and thereby developing drugs that may
address unmet patient needs. It has been argued that the development of personalized medicines could contribute to the creation of sustainable economic markets for pharmaceuticals while addressing public health concerns associated with drug safety and efficacy [Service, R.F. 2004; Ozdemir, V. 2006a].

Since late 1990s, pharmacogenomics and other high throughput -omics biomarker technologies (e.g., transcriptomics, proteomics, metabolomics, nutrigenomics) have been introduced to make the drug development process more innovative and predictable [Ozdemir, V. and Godard, B. 2007]. However, the diverse short and long term impacts of -omics technologies on the pharmaceutical industry infrastructure and viability, in particular the socio-ethical and economic challenges of their implementation in pharmaceutical research have not been adequately studied [Hedgecoe, A.M. 2003; Hedgecoe, A. 2004; Corrigan, O.P. 2005]. It is not at all clear that pharmacogenomics will necessarily stimulate growth of the pharmaceutical industry. And even if this were to be the case, such growth might well require a qualitatively different approach, i.e., one that favours long term economic sustainability over immediacy of financial returns [Williams-Jones, B. and Ozdemir, V. 2008 in press; Ozdemir V. and Williams-Jones, B. 2006; Mintzes, B. and Lexchin, J. 2005].

The integration of -omics technologies in drug discovery and clinical development also poses serious challenges for responding to financially overly burdened health care systems, and growing public demand for social/distributive justice and equity in access to essential medicines [Quick, J.D. 2003; Ozdemir et al., 2006a].

The present paper aims to address these challenges by first identifying their distinctive features and then situating them in their broader social, economic and political contexts in order to highlight their complexity and interrelatedness. When applicable, we will draw upon examples from diverse markets (e.g., the automobile industry and ‘green’ commodities) to help consider the responsibilities of corporate directors to shareholders, and of shareholders to the broader civil society, and to suggest ways of integrating the concept of sustainability into corporate and investor models of pharmaceutical industry development. Finally, we submit that fair trade and sustainable economic prosperity can co-exist with an equitable and ethical approach to drug development and commercialization of personalized medicines. It is our hope that this discussion will spur further reflection by readers on previously neglected socio-ethical dimensions of personalized medicine and point to constructive and concrete ways forward for the ethical integration of pharmacogenomics and other -omics technologies into drug development and clinical practice.

THE PUBLIC HEALTH RATIONALE FOR PERSONALIZED DRUG THERAPY

Personalized medicine is often associated with the rational choice of medicines and/or the customization of drug doses to individual patient characteristics. The goal of personalized medicine, in this sense, is tied to treatment success, predictability of health outcomes and ultimately, to health promotion and individual well-being. The notion of personalized medicine reflects, however, a fundamental conceptual departure from the traditional approach to pharmacotherapy which applies drugs uniformly to broad patient populations rather than to smaller subpopulations where drugs may exhibit enhanced efficacy and safety [Ozdemir et al., 2001]. The overarching public health rationale for personalized medicine is based on three fundamental concerns: (1) drug efficacy, (2) drug safety and (3) innovation rates in drug discovery.

First, a review of the published data on the major drug classes prescribed for common human diseases concluded that response rates vary substantially across therapeutic areas, ranging from 30% in the case of drugs directed at Alzheimer’s disease to 80% for analgesics such as the Cox-2 inhibitors [Spear, B.B. et al., 2001]. Thus, the proportion of patients who respond positively to their medications is only about 50%, which implies that the other 50% of the population is not receiving proper medications or is suffering from marked therapeutic delays by switching from one medication to another until appreciable clinical benefit is attained.

Second, without reliable predictors of drug effects, serious and fatal ADRs can occur. A study on variability in drug safety demonstrated that in the United States alone, approximately 2 million hospitalizations and 106,000 deaths per year can be attributed to ADRs, making them the fourth leading cause of death in this country [Lazarou, J. et al., 1998; Drews, J. and Ryser, S. 1997]. Customizing medical practices through individualized drug development and choice of prescriptions could thus help reduce the very high incidence of ADRs and therapeutic failure.

A third rationale for personalized medicines is the molecular heterogeneity of drug targets and human diseases. Current drug targets across all therapeutic areas amount to only about 500 molecular targets (e.g., receptors) [Drews, J. and Ryser, S. 1997; Drews, J. 2000]. Considering the diversity of human diseases and molecular heterogeneity in common complex diseases such as cancer and diabetes, there is no doubt that the molecular targets associated with these diseases are far greater in number. Hence, the treatment with blockbuster drugs will need to be replaced by targeted therapies in order to respond appropriately to the molecular heterogeneity of human diseases. This molecular diversity may not be static over a disease lifetime or disease course, and may in fact be a moving target producing currently unrecognized variable disease subtypes with the same clinical phenotype, or variability in disease staging and severity. However, the number of New Drug Applications (NDAs) approved by the US FDA between 1990-2004, and the percentage of breakthrough New Molecular Entities (NMEs) that offer significant improvements compared to already marketed products, have remained remarkably low (Fig. 1) [Ozdemir, V. and Williams-Jones, B. 2006; FDA, 2004]. Increasingly, those drugs introduced in the clinic are ‘me-too’ compounds that vary only enough in pharmacologic structure or profile to obtain patent protection. The low innovation rate in drug development, in a context of high incidence of ADRs and limited drug efficacy, thus raises important socio-ethical and health policy questions regarding the utility and merit of continuing to develop uncustomized blockbuster drugs that overlook the molecular or other (e.g., social) heterogeneity underlying specific diseases.
PHARMACOGENOMICS AS A TECHNOLOGY PLATFORM TO ACHIEVE PERSONALIZED DRUG THERAPY

Pharmacogenomics is a term that was introduced in the late 1990s to broadly define the study of genetic factors, both in gene sequence and gene expression, involved in individual variability in drug safety and efficacy [Giacomini, K.M. et al., 2007; Eichelbaum, M. et al., 2006; Evans, W.E. and McLeod, H.L. 2003]. This new concept has its origins in pharmacogenetics which dates from the 1950s and refers to hypothesis-driven investigations on a specific or limited number of candidate genes in relation to individual differences in drug metabolism [Motulsky, A. 1957; Kalow, W. 1962]. We here use the term pharmacogenomics, but much of the following discussion and concepts also apply to pharmacogenetics.

We stress that it is unrealistic to expect that individual variability in drug treatment outcomes will be wholly attributable to genetic causes. The power of pharmacogenomics to achieve what it promises and to serve as a basis for personalized medicine and drug development still remains unclear, particularly with regards to the development of new drugs for complex disorders, which are the very illnesses that pose the greatest public health challenges. Nonetheless, current understandings of genetic variations in drug metabolism and elimination pathways (i.e., pharmacokinetics) and drug targets, not to mention genetic contributions to human diseases, collectively suggest that pharmacogenomics can be an important tool for discerning the mechanisms involved in highly variable drug therapy outcomes, and thus potentially help remedy the low innovation rates in drug development noted above. Indeed, recently an association of 50 research groups has identified 24 risk factors for 7 major common diseases – e.g., hypertension or type 1 and type 2 diabetes – through the use of high-throughput genomics technologies, confirming that such new biomarker technologies can be a powerful tool for the rapid assessment of genetic contributions to human diseases. This approach thus provides new and exciting lines of investigation for research and development of drugs targeted towards specific genomic risk factors [Bowcock, A.M. 2007; Consortium, 2007].

Pharmacogenomics has been more easily integrated into the research and development programs of smaller biotech companies than the larger pharmaceutical companies, with the result that every year a growing number of new biotech drugs are entering the pharmaceutical market. New drugs produced by small biotechnology companies have even reached blockbuster drug status, with innovations such as monoclonal antibodies (mAbs) used in cancer treatment (e.g., bevacizumab from Genentech and cetuximab from ImClone System) or new HIV combination treatments (e.g., emtricitabine and tenofovir) [Lawrence, S. 2007]. The interest in these biotech companies has thus understandably been increasing, giving rise to new partnering between big pharma and the smaller biotechs [Moran, N. 2007]. But as illustrated by the still low innovation rate for NME’s following the introduction of biotech drugs into the pharmaceutical market (Fig. 1), the expansion of the biotech drug market has proven to be much less successful than predicted [Joppi, R. et al., 2005; Nightingale, P. and Martin, P. 2004]. Hence, the use of pharmacogenomics in drug development will have to concentrate on research for new molecular targets or untreated diseases, and not on the production of ‘biosimilars’ – understood here as ‘me-too’ personalized drugs – if higher innovation rates are to be attained with this technology.

RE-THINKING THE DRUG DEVELOPMENT PROCESS AND THE PHARMACEUTICAL INDUSTRY

The major pharmaceutical companies are facing increasing pressure to discover new drugs that will help compensate for recent losses of patent protection on blockbuster drugs, and withdrawals of drugs from either the market or the development pipeline. For example, the loss of patent protection on two blockbuster drugs – the antidepressant sertraline and the antibiotic azithromycin – resulted in substantial reductions in sales for these drugs, an economic situation that was worsened by the December 2006 announcement that the hitherto promising drug candidate torcetrapib was being withdrawn from further clinical development because of significant ADR risks; this candidate drug was intended to replace the anti-ldemegic agent atorvastatin, which will soon be facing generic competition. Moreover, not only are companies having to deal with low innovation rates and pre-market withdrawals, many companies have also experienced extremely costly ($Billions in US class action suits) post-market withdrawals, notable examples being rofecoxib in 2004 [Merck, 2004] and the forced withdrawal of valdecoxib in 2005 [FDA, 2005].

The blockbuster model of drug development – which until the 1990s was able to sustain double digit revenue growth for the pharmaceutical industry – is failing [Angell, M. 2004; Kelly, M. 2002]. Patent expirations, lack of breakthrough NMEs, and costly drug withdrawals all point to the inherent weakness of concentrating expectations on ‘one product basket’, and of not keeping up with the diversification of therapeutic candidates in the pharmaceutical pipeline. Although the blockbuster model can significantly maximize the profits from a given drug candidate, it also concentrates the attendant financial risks of production failures or market withdrawal of drugs. Such a clustering of products increases the costs of development and testing for limited additional social benefits, while also raising the risk of a ‘domino effect’ where the failure or withdrawal of one drug in a class provokes the withdrawal of other drugs that share the same mechanism of action or toxicity.

While pharmacogenomics technologies do offer the promise of increased innovation in upstream fundamental biological research – such as discovery of disease-causing genes and novel drug targets – therapeutic products developed with pharmacogenomics guidance for narrowly-defined patient subpopulations may also be the cause of considerable trepidation for the industry [Williams-Jones, B. and Corrigan, O.P. 2003; Smart, A. et al., 2004; Sinha, G. 2006]. The primary costs of drug production lie in the fixed costs of research, development and testing. But targeted therapies by definition offer benefits for smaller populations resulting in essentially fragmented markets. Hence, their potential revenue streams are smaller, with lower potential sales over which to spread the fixed costs. However, as we will discuss below, these low potential revenues and sales could be po-
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tentially overcome by an increase in sustainability of such targeted therapies, translating into longer market availability for customized drugs as compared with blockbuster drugs (Fig. 2).

In the context of disease- and patient-specific market fragmentation, where there may be multiple subpopulation-specific drugs for a single disease category, or multiple subcategories of a major disease, pharmaceutical companies and their key blockbuster drugs will no longer only have to compete with other me-too drugs, but will also have to go up against targeted and thus more safe and effective drugs within a particular drug-disease class. Hence, the advent of targeted drug therapies developed with pharmacogenomics tests also has the potential to seriously curtail off-label sales of brand name drugs (a common although ethically contested practice and an important source of revenue for the pharmaceutical industry) [Lurie, P. et al., 2005; O’Reilly, J. and Dalal, A. 2003] because individual physicians would have less motivation – or even lack the authority – to prescribe drugs for off-label use. Targeted personalized drug therapies could thereby threaten the potential market expansion of me-too and brand name drugs. On the other hand, the losses to

Fig. (1). Innovation rates in drug development. New Drug Applications (NDAs) approved in calendar years 1990–2004 by the FDA, and NMEs subjected to priority regulatory review while offering a significant improvement compared with marketed products in the treatment, diagnosis or prevention of a disease. Innovation in drug development is defined as the percentage of these breakthrough NMEs in relation to all NDAs approved in each calendar year – [Modified from Ozdemir, V. and Williams-Jones, B. 2006].

Fig. (2). Projected relationships between the degree of customization of drug therapy and sustainability in the health care market. Blockbuster drugs (e.g., Vioxx) have low degree of customization; they tend to provide high and immediate large profits but risk a more limited time on the market due to potential for costly post-marketing withdrawals and low sustainability. For highly individualized treatments (e.g., personalized cancer vaccines), the profit potential can prove to be low in the immediate years following market introduction. But with customized treatments, profit potential increases with more years on the health care market and through lateral gains such as improved consumer and public trust in customized medicines. These relations collectively suggest that the profitability motives can be effectively engaged with both personalization and sustainability of drug therapy. The financial success of Herceptin as a customized drug treatment attests to this concept.
patients due to ADRs, lack of efficacy and delay in effective therapy, which could conceivably be reduced significantly by personalized therapies, are not generally taken into account in pharmaceutical market analysis, despite the fact that they are part of the social cost-benefits balance. Both individual patients and public health programs inevitably suffer consequences without compensation, which should serve as a disincentive (e.g., with a view to being a responsible corporate citizen) for companies to develop generalized undifferentiated therapies based on the blockbuster model. But while the industry recognizes that the future profitability of the heretofore extremely profitable blockbuster model will decline, a departure from this model poses serious challenges for company directors and investors.

Pharmacogenomics and other -omics technologies were welcomed by big pharma as a means to facilitate upstream drug discovery oriented applications and to secure future market exclusivity of new blockbuster drugs through identification of novel drug targets [Service, R.F. 2004; Ozdemir, V. 2006b; Eisenberg, R.S. 2002; Fourie, J. and Diasio, R. 2005; Tardif, J.-C. et al., 2006]. However, recent qualitative research by social scientists (interviews with large pharma and biotech company representatives), indicates that pharmacogenomics is being used primarily for internal decision-making in preclinical and clinical drug development, notably for the elimination from the pipeline of compounds subject to genetically polymorphic metabolism, instead of further development in genotype-stratified clinical trials [Hedgecoe, A. 2004; Sinha, G. 2006]. Importantly, pharmacogenomics is also being used to identify disease genes as targets for new drugs, but such discoveries do not, in-and-of-themselves, lead to personalized therapeutics unless predictive pharmacogenomics tests are proactively co-developed together with new drug candidates. Thus not surprisingly, not all pharmaceutical companies (nor even all departments within a large pharma) are uniformly enthusiastic about pharmacogenomics applications [Williams-Jones, B. and Corrigan, O.P. 2003].

A tension exists between (1) the desire for the discovery of new drug targets to secure new patents and recover benefits for an underserved subpopulation, and (2) the potential fragmentation of the pharmaceutical market that reduces the profitability of existing or new drugs. This uncertainty engenders much ambivalence and anxiety within the large pharma companies that may be tempted to integrate pharmacogenomics into their drug development processes. For example, in the words of the director of the clinical genetics unit of a large pharma “…in our company we’ve never done anything like this before. And that’s certainly viewed with suspicion. The pharmaceutical industry is not the most responsive to change” [Williams-Jones, B. and Corrigan, O.P. 2003].

Representatives of large pharma companies frequently respond that only drugs with large-scale markets allow for the recovery of the high research and development costs for new medications. However, critics have noted that the estimated research and development costs are often exaggerated [Light, D.W. and Warburton, R.N. 2005], raising two major issues: do research and development costs prohibit a market rate of return on investments in targeted therapies, given the true risk of such development; or are the risks overestimated by producers and investors? Secondly, can targeted therapies be part of a more sustainable business model that can provide an acceptable profit/risk combination for investors in the long run, given the reduced risk in such targeted therapies for post-marketing drug withdrawals? The recent successes (blockbuster and even ‘super blockbuster’) of smaller biotech drugs and targeted therapies such as Herceptin attest to the promising market potential and public demand for such improved therapies [Lawrence, S. 2007]. These targeted therapies, intended for smaller subpopulations of patients, may also make the me-too culture of drug development less desirable due to competition in smaller markets, and thus further cultivate a constructive socio-economic context for drug innovation.

In the subsequent sections, we examine two concepts, (1) sustainability and (2) corporate social responsibility, a deeper appreciation of which, we suggest, can help resolve some of the aforementioned anxieties about market fragmentation and innovation in upstream drug discovery and clinical drug development.

**SUSTAINABILITY AND PERSONALIZED MEDICINES: LESSONS FROM GLOBAL WARMING, THE KYOTO PROTOCOL AND HYBRID CARS**

Sustainable development is generally defined as development that possesses the ability to address local needs in the present while preserving the ability to meet the anticipated system-wide needs in the future [Martens, P. 2006]. In other words, sustainability is a successful balance between the short term consequences of present actions taken by a given stakeholder (e.g., individuals, scientists, companies or governments) and their long term and broader consequences for a larger group of stakeholders (e.g., global civil society). Sustainability as a concept was derived from analyses of long term changes in ecosystems, but also applies to economic and socio-cultural developments. The concepts of sustainable development and sustainability are now closely linked to government promises and policies, as was illustrated recently with the interest for investing in ethanol production as a means to reduce oil consumption and dependency [Thomas, K. 2007; Wald, M.L. 2007], and have garnered particular attention as a possible response to global warming.

Unfortunately, it now appears that a failure to appropriately consider sustainability in the issue of global warming has undermined the ability of some governments, both in the North and the South, to strategically position themselves to achieve the putative long term goal. For example, the US federal government decision not to participate in the international Kyoto Protocol for the reduction of greenhouse emissions was based in large part on the grounds that such mandatory reductions would jeopardize US businesses and impede continued economic development. By failing to acknowledge the serious social, economic, environmental and political threats posed by global warming – the science of which is now overwhelmingly endorsed by the international scientific community – has meant that the US is largely unprepared to take advantage of infrastructure changes in the global economy or be a leader on the international stage.
In 2004-05, the US investment community recognized that the US could have benefited by participation in the international trade in marketable permits for greenhouse gas emissions. Currently, policy proposals are ‘playing catch-up’ in redirecting economic development to address necessary changes in construction, energy, and transportation to avert global warming. Individual states have moved to implement sustainability policies that reconcile environmental protection with financial concerns, most notably California, with its Bill 32 (September 2006) that set a global warming emission cap [Kammen, D.M. 2006], and its Environmental Preferable Purchasing (EPP) contract code enforcing the governmental obligation to preferentially purchase green products. Indeed, a major incentive for California’s interest in implementing anti-global warming laws has been the social and economic benefits that investment in a green economy can provide, notably in terms of job creation and the export of ‘green’ products and technologies [Asmus, P. 2006; Kammen, D.M. 2006]. Similar arguments are at the heart of recently implemented European and UK policies.

Another related example is the failure of major automobile manufacturers to embrace the technological opportunities of more environmentally friendly vehicles. Underlying public demand for quality cars with innovative designs and lower energy needs (e.g., hybrid cars) has been long ignored by General Motors (GM), Ford and DaimlerChrysler. Despite clear indications of future increases in oil prices and pollution costs, these automakers focused on fighting policy initiatives to increase fuel-efficiency, including heavy lobbying against fuel-efficiency standards and the suppression of promising technologies such as electric and hybrid vehicles, ostensibly to avoid competition with existing less efficient technologies. Japanese automakers, on the other hand, seized the opportunity to deliver quality products and generate new business by actively investing in hybrid cars that had been labelled initially as ‘unprofitable’ [Gertner, J. 2007]. Consequently, the aforementioned US automakers lost a major part of their local and global market share to Japanese automakers, allowing Toyota to become the third biggest auto seller in the US in 2006 [Gertner, J. 2007; Krisher, T. 2007; Maynard, M. and Warner, F. 2006]. Hence, this loss of market share can partially be attributed to the usual response of car model failure, which has been to replace it with a bigger or more luxurious me-too model in hopes of producing the next ‘blockbuster car’ instead of investing in innovative alternative technologies.

So what can the pharmaceutical industry learn from California, ‘green states’, and hybrid vehicles? The emerging market for personalized medicines is not simple or readily discernible, as is increasingly becoming obvious for investments in environmentally friendly technologies. Unlike, Toyota and the hybrid car, there is no guarantee that pharmacogenomics and customized therapies will uniformly lead to sustainable pharmaceutical products in all cases. Drug toxicity and treatment failures are complex multifactorial phenotypes that are attributable to both genetic and environmental factors as well as complex gene-environment interactions that are often incalculable or unpredictable. Nonetheless, as we will argue below, the approach taken by Toyota and California can serve as a model, and even a market precedent, for the integration of pharmacogenomics into drug development.

First, progress towards a sustainable economy could not have been achieved without clear recognition that the social benefits of emissions reductions could, through rational long term policies, enable private markets to capture those benefits so that environmental preservation and a sustainable economy could develop in tandem. The pharmaceutical industry should work to be ‘ahead of the curve’ in responding to a changing economic and political context. A fiscal myopia that focuses on economic returns or that neglects broader social and policy issues can be extremely damaging to commercial viability. By contrast, attention and responsiveness to important public health challenges, such as the need for better, safer and more accessible medications, and a view to innovation and lateral thinking, can enable companies to become leaders in the competitive pharmaceutical drug markets. That is, the pharmaceutical industry could learn from Japanese automaker’s success by shifting development from an ‘emergency re-active response’ approach to one that is long term, pro-active and sustainable. This sustainability, as mentioned before, does not rely solely on environmental considerations. In the particular context of the pharmaceutical industry, sustainability entails both social and economic responsibilities. Hence, investment in a new drug development technology like pharmacogenomics – or in personalized medicine in the clinic (i.e., not only in upstream research in drug discovery) – could respond to these sustainable criteria in order to insure greater chances of survival and success for the industry.

Second, the general public – as citizens and also shareholders in business – is increasingly asking political and economic leaders to embrace a responsible and accountable mode of action, which translates into socially responsible environmental laws. The influence of the public or consumers, thus, should not be underestimated in future projections of personalized drug development. Failure to self-critique and adjust to the new realities resulting from public demands can mean extreme difficulties for long term industry welfare and viability. This is particularly apparent when uncustomized blockbuster drugs are withdrawn from the clinic with a resulting loss of public confidence and revenue, and increasing consumer frustration with expensive pharmaceuticals that have safety risks or limited efficacy.

A recent convincing example of the important role of publics and policy makers in shaping pharmaceutical policies is US Senator Barack Obama’s proposed Genomics and Personalized Medicine Act of 2006 [US, 2006]. This proposal, should it be enacted, would establish a Genomics and Personalized Medicine Interagency Working Group within the US Department of Health and Human Services to coordinate personalized medicine efforts, provide $150 million to support research on genomics, offer a 100% tax credit for pharmacogenetic tests to improve drug safety, and create a US Biobanking Research Initiative similar to efforts in other countries (e.g., Sweden, Canada, the UK) [Goddard, B. et al., 2004; US, 2006]. As in the case of growing public support for funding of green technologies as a response to concerns about global warming, political support for pharmacogenom-
ics R&D would provide a significant incentive for those biotech and pharma companies involved in developing personalized medicines; it also says a great deal about the public and political desire for the more rapid introduction of personalized medicines.

As discussed previously, a responsible approach to market fragmentation following the introduction of pharmacogenomics in drug development could help meet the need for economic sustainability, but how can a socially responsible sustainability be achieved?

**SOCIAL RESPONSIBILITY AND PHARMACOGENOMICS: WAYS TO REMEDY INEQUITIES IN PATIENT CARE AND INTERNATIONAL HEALTH**

**Responsibility as a Socio-Ethical Construct: A Conceptual Foundation**

Responsibility is a social relationship, but one defined by the moral rights that all individuals possess vis-à-vis one another. The basis of responsibility is therefore reciprocity, and the affirmation and defense of the rights of individuals. The philosopher Hans Jonas, in his book *The Imperative of Responsibility*, extended this to future generations, to solidarity. He argued for the fact that the position of human beings in the modern world and the possible domination of nature in industrial society have changed the ethical obligations of human beings [Jonas, H. 1985]. The duty to protect vulnerable and fragile life is an imperative of responsibility. Continuing in the tradition of Kant, Jonas recreates the categorical imperative to include an imperative for existence itself, “act so that the effects of your action are compatible with the permanence of genuine human life” [Jonas, H. 1985]. The moral responsibility of the individual is no longer confined to his lifetime or even to his direct actions. In a sense, to adopt this new imperative is to view the growth of responsibility as proportional to the growth of human power. Therefore the principle of responsibility is the foundation for the formulation of basic ethical principles that go beyond a pure utilitarian pragmatism.

The extension of the notion of moral responsibility to social responsibility implies that society, through its stakeholders, must continue to protect and care for individuals, which in previous generations was a question of private activity or was delegating to social institutions such as the church and the medical profession. Social responsibility implies that stakeholders, in light of the vision of respect for autonomy, dignity, integrity and vulnerability, are conscious of the consequences of their own actions. Such a responsibility implies a duty to take care of the weak, the poor and the sick people in society. By extension, corporate social responsibility emerges from a realization among transnational corporations of the need to account for and redress their adverse impact on society: specifically, on human rights, labor practices, and the environment.

Generally, corporate social responsibility can be understood as the socio-economic product of the organizational division of labor in complex modern society, such that as major actors in society, they (e.g., pharmaceutical industry) have a concomitant responsibility for other stakeholders, be they citizens, consumers, communities or even nations [Leisinger, K.M. 2005]. Corporate social responsibility is closely linked with the principle of sustainability, which argues that corporations should make decisions based not only on financial factors, but also based on the long-term social and environmental consequences of their activities. But whether it is moral or social or corporate social responsibility, global society through the Universal Declaration on Human Rights has explicitly articulated the fundamental obligations we all have to help others in need because of respect for the dignity of others. Consequently, drug company managers arguably have moral responsibilities to society that go beyond mere social responsibility to provide charity [De George, R.T. 2005].

In a 2005 special issue of the Business Ethics Quarterly dedicated to the private and societal ethical responsibilities regarding drugs, patents and health, De George, Werhane and Gorman describe drug companies as the beneficiaries of vast public and private bio-medical science and health networks in society that enable their innovative and marketing activities. De George argues that drug company managers owe society a “Production Obligation”, that is, that they will use their know-how to innovate new drugs to alleviate disease (even for diseases that will not recoup investments) and improve health; second, they have an “Access Obligation” to provide medicines for those in dire need [De George, R.T. 2005]. Access to needed medicines having a great deal to do with price, De George points out that most governments around the world use tools of government policy to impose limits on drug prices, indicating a widespread societal willingness to facilitate (and even demand) favorable access to drugs in national health care systems. Furthermore, drug managers should find a new “moral imagination” that leads to drug discounts and donations to the world’s neediest, to the dissemination of their know-how regarding drug therapies and to drug distribution cooperation with public authorities and non-governmental organizations [Werhane, P.H. and Gorman, M. 2005].

On the other hand, others would argue that global poverty and poor health conditions are the primary responsibilities of the world’s national governments and international governmental organizations (e.g., the UN, WHO), which possess the social and political mandates, and appropriate organizational capabilities, to improve global health outcomes [Leisinger, K.M. 2005]. According to Leisinger, private enterprises have neither the societal mandate nor the organizational capabilities to provide health care to the sick in their home countries or in the developing world. Nevertheless, he recognizes that private enterprises do have responsibilities to society that can be categorized as *what they must do*, *what they ought to do*, and *what they can do*; the challenge, then, is negotiating what these responsibilities entail in the practice of drug development and delivery.

**Public Demand, Globalization and the Shaping of a New Market Reality**

The utility of particular personalized medicines will be modulated by the population concerned, thus it is important to question the specific needs of individuals and communities for pharmacogenomics or other -omics technologies. In the context of pharmacogenomics applications, the limiting
factor becomes the identification of the potential user population for a given medicine. Given the increasing ease in migrating across geographical, political and cultural boundaries, populations are becoming more fluid and genetically admixed; traditional scientific categories of race, ethnicity, or geographic origin have less specificity and thus less utility. How then is this heterogeneous population reality translated in the drug market, and what impact will it have on the pharmaceutical industry and development of personalized medicines?

Global pharmaceutical markets will have to respond to these heterogeneous and geographically diverse populations, as well as the growing demand for safer and more effective personalized medicines. As was previously illustrated with the automobile industry, a reticence to respond to changing public demand and international interests can lead to a loss of local and global market share. The pharmaceutical development process is not immune to this new market reality, and is starting to adjust to the emerging needs of a more complex consumer population. Attention to broader global health needs, we suggest, can be a useful means by which the pharmaceutical industry can better respond to evolving health concerns while also ensuring economic sustainability.

Traditionally, most new drugs have been developed to treat those diseases prevalent in the wealthy countries of the North; little effort has been made to address the needs of developing countries of the South (e.g., vaccines, treatments for infectious diseases). The actual context of drug development is illustrated by the ‘90/10 divide’, where 90% of the global research resources are utilized for 10% of the world population, i.e., the developed countries [Hale, V.G. et al., 2005]. Similarly, 90% of the world population is at risk from infectious diseases, yet only 10% of the world’s research and pharmaceutical resources are spent on them. Taking into consideration that one third of the world population does not have access to the medications they need, and that this proportion rises to half of the population in the poorest regions (parts of Africa and Asia), it becomes obvious that drug accessibility constitutes an important issue of global justice and social responsibility [Hale, V.G. et al., 2005]. If pharmacogenomics and other -omics technologies are to contribute to socially responsible sustainability, the issue of globally relevant drug development will have to be addressed.

**Social Responsibility and Patient Care**

One could say that social responsibility is the core challenge that scientists are trying to address with the establishment of pharmacogenomics and the new -omics technologies in drug development and patient care. Indeed, the promise of increased efficacy and safety for patient care that could result from personalized medicine is about ensuring more responsible practices in medicine [Moldrup, C. 2002]. The association of genetic variability with disease development has enabled the understanding of important monogenic diseases, such as cystic fibrosis [Dinwiddie, R. and Crawford, O. 1993] or sickle cell anaemia, but can such associations be useful in the study of complex diseases such as cancer or diabetes that implicate a multitude of genes and complex gene-environment interactions? If so, will the integration of pharmacogenomics and other -omics technologies in drug development and prescription processes render medical practices more responsible?

The discovery of genes associated with specific diseases provided great hopes in the field of medical genetics, showing that the identification of these genes could contribute to novel diagnostics and treatments for rare diseases. But since most human diseases seem to result from multigenic events or interactions, it quickly became apparent that the simplified biological dogma – according to which each disease could be associated with a modified protein encoded by a gene variant – could not account for all known diseases or explain a large portion of variability in susceptibility to diseases. In diseases such as cancer, there is also the added complexity of multigenic events and interactions that occur in the tumours as well as host genomes which may produce variability in susceptibility to cancer and disease outcome. Even for monogenic diseases such as cystic fibrosis, the dream of gene therapy cures has yet to materialise [Lee, T.W.R. et al., 2005], leading to critiques that the potential of these technologies has largely been ‘hype’. It is clear that genetic information, and the new -omics technologies, will be insufficient to realize the promises of curing rare or common diseases [Hedgecoe, A. and Martin, P. 2003]. For pharmacogenomics (and other -omics technologies) to escape the charge of contributing to medical ‘hype’, their integration in the drug development process must be balanced and justified, such that the rationale for their use, advantages, and limitations are made explicit.

**A World Health Organization Framework for Responsible Action on the ‘Top 10’ Unmet needs in International Health: A Role for Pharmacogenomics?**

A brief look at the variations in the Top 10 leading causes of deaths according to countries’ relative wealth (Tables 1 and 2) highlights the fact that the health needs of populations are strongly influenced by levels of wealth. The WHO classification of leading causes of death for 2002 (and the projected numbers for 2005), show that infectious tropical diseases – HIV/AIDS, diarrhea-related diseases, tuberculosis and malaria – have claimed more deaths in low-income countries (in millions) than the total amounts of deaths in the high-income countries for the same period [WHO, 2007b]. The concept of a specific financial burden on accessibility to health, as discussed by public health scholars such as Jonathan Mann [Mann, J. 1998], can in part be understood in terms of restricted capacities to purchase drugs in a low-income context. Knowing that an important part of the world population lives on less than $2/day, the issue of difficulties in equitable access to drugs becomes of utmost importance.

Poor access to medicines is not solely due to the high costs of drugs; it often results from a lack of effective and safe medicines on the market or in the pharmaceutical developmental pipeline. The increased financial risks of unattractive markets and the high costs associated with the development of new drugs have been evoked to explain the pharmaceutical companies’ trepidation with regards to developing drugs that target specific tropical or rare diseases. Acknowledging these neglected diseases will be a crucial step in achieving social responsibility in the drug development and distribution process. But, how can pharmacogenomics facili-
It has been widely proposed that pharmacogenomics and other -omics technologies will bring down the overall cost of drug development and contribute to research on rare diseases or health predicaments affecting low income countries [Daar, A.S. and Singer, P.A. 2005; Singer, P.A. and Daar, A.S. 2001]. Since genomic knowledge can be qualified as a global public good [Acharya, T. et al., 2004], its use should not be restricted to diseases that affect the populations of wealthy countries but should also aim to address global health needs [Pang, T. and Weatherall, D. 2002]. Including pharmacogenomics technologies in the drug development process could then help reduce global health disparities by optimizing drug efficacy and safety for the diseases most affecting the developing world [Pang, T. 2003].

Reducing the drug accessibility gap has been a long-standing social preoccupation for many groups and organisations. One of the first attempts to tackle this problem led to the establishment of a Model List of Essential Drugs by the WHO in 1977, drug donations programs, and more recently to the birth of not-for-profit pharmaceutical companies ori-


<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of Deaths (Millions)</th>
<th>Percentage of Deaths (%)</th>
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<tbody>
<tr>
<td></td>
<td>2002</td>
<td>2005</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.34</td>
<td>1.38</td>
</tr>
<tr>
<td>Stroke and other cerebrovascular diseases</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancers</td>
<td>0.46</td>
<td>0.47</td>
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<tr>
<td>Lower respiratory infections</td>
<td>0.34</td>
<td>0.34</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Colon and rectum cancers</td>
<td>0.26</td>
<td>0.27</td>
</tr>
<tr>
<td>Alzheimer and other dementias</td>
<td>0.22</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.15</td>
<td>0.15</td>
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<tr>
<td>Stomach cancer</td>
<td>0.14</td>
<td>0.15</td>
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<tr>
<th>Disease</th>
<th>Number of Deaths (Millions)</th>
<th>Percentage of Deaths (%)</th>
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<tbody>
<tr>
<td></td>
<td>2002</td>
<td>2005</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>3.1</td>
<td>3.29</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>2.86</td>
<td>2.72</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2.14</td>
<td>2.06</td>
</tr>
<tr>
<td>Perinatal conditions</td>
<td>1.83</td>
<td>1.78</td>
</tr>
<tr>
<td>Stroke and other cerebrovascular diseases</td>
<td>1.72</td>
<td>1.83</td>
</tr>
<tr>
<td>Diarrhoeal diseases</td>
<td>1.54</td>
<td>1.48</td>
</tr>
<tr>
<td>Malaria</td>
<td>1.24</td>
<td>0.87</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.1</td>
<td>1.01</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>Road traffic accidents</td>
<td>0.53</td>
<td>0.60</td>
</tr>
</tbody>
</table>
ent towards R&D for tropical and neglected diseases [Hale, V.G. et al., 2005; Brewster, A.L. et al., 2005]. Although these initiatives are laudable, further science policy measures are needed such that new drugs developed with pharmacogenomics guidance can also be considered for future incorporation in the Model List of Essential Drugs [Reidenberg, M.M. 2007]. At the same time, it would be unrealistic and naive to expect that pharmacogenomics will markedly transform health care delivery and address all unmet needs. Other factors, such as transparency and accountability in local governments and governance structures, can be equally if not more important in improving the health of persons in developing countries.

**How can Social Responsibility Translate into Market Sustainability?**

There is increasing evidence that being a socially responsible company can be good for business. More than just a marketing ploy, there may be opportunities for 'strategic altruism' whereby a private enterprise openly supports a public good that is also in its own interests.

Public dissatisfaction with current drug pricing, and the related issue of drug accessibility for impoverished populations, may affect long term corporate sustainability, most notable in the uptake of generic drugs by developing countries [Hogerzeil, H.V. 2004] or Wal-Mart’s announcement that they will sell generic drugs [Kavilanz, P.B. 2006]. In the face of high drug prices and limited resources, populations may also resort to more dangerous options, such as black-market drugs, brand-name copies, substandard drugs or off-label use. These undesired social and public health issues are a side effect of the dominant ‘blockbuster’ drug model.

One way of responding to this loss of trust would be to take a much more pro-active role in the promotion of global health by focusing drug R&D in part on orphan diseases. Drug donation programs for diseases specific to certain tropical regions – such as Merck’s donation of ivermectin for the treatment of river blindness or GlaxoSmithKline’s donation for malaria treatment [Molyneux, D.H. and Nantulya, V. 2005; Reich, M.R. 2000] – are a positive step, but still far too limited in scope or impact to change public opinion and perceptions concerning equitable access to medicines.

Another important progressive shift would be to recognize that consumers of pharmaceutical products – mostly represented by legislators, public or private health insurers, or medical associations – are entitled to demand value for money. In a context of me-too drugs, clinicians, patients and health insurers are forced to choose from products that differ very little in terms of quality or price, and will thus have a strong interest in opting for lower cost or even generic versions. Yet when personalized medicines are offered, consumers will likely choose according to a number of characteristics such as quality, utility, risk-benefit, and price; moreover, they may be willing to pay more in exchange for greater benefits, when compared to me-too drugs.

From the perspective of pharmaceutical companies, it may become more cost-effective and profitable to focus on developing innovative drugs that increase the efficacy and safety of drug response, instead of exponentially raising the investments in marketing strategies which limits the funds for R&D and makes it harder for companies to gain long term consumer trust [Brennan, T.A. et al., 2006; Lexchin, J. 2005; Mintzes, B. and Lexchin, J. 2005]. Moreover, given the buying power of private and public health insurers (e.g., particularly in Canada, Europe and the UK), a company that can convince consumers (i.e., insurers) that their product is genuinely more effective for a specific population may be able to generate greater financial returns on their R&D investment.

**CONCLUSIONS AND FUTURE OUTLOOK**

Recent events such as marked reorganizations and mergers in the pharmaceutical industry, drug withdrawals (either from the market or the drug development pipeline) and expiry of blockbuster drug patents are all symptoms, we suggest, of the need for a fundamental conceptual shift in the drug development process and long term goals. There is a need to acknowledge the many complexities that characterize disease pathophysiology, drug response and the increasingly global drug market [Quick, J.D. 2003; Sheiner, L.B. 1989, 1991, 1997]. While informed consent and DNA banking, for example, remain important bioethics issues in pharmacogenomics research and development, there is a serious risk in limiting socio-ethical reflection only to these topics. There is a need for an earnest attention to the social responsibility of the pharmaceutical industry, and the lessons that can be learned from other industries that successfully incorporated social responsibility and sustainability into their product development processes. To the extent that personalized medicine is about improving population health in a predictive and reliable manner, it appears logical to consider sustainability as a core bioethics construct in pharmacogenomics and more broadly, in predictive medicine and international health [Williams-Jones, B. and Ozdemir, V. 2008a, 2008b; Dwyer, J. 2005].

The integration of pharmacogenomics and associated -omics technologies in the drug development process could constitute a starting point in this regard. An increase in drug labels containing pharmacogenomics information has been observed over the last decade, in part due to the leadership and encouragement by regulatory agencies [CDER, 2006]. Although it is not impossible that genomic considerations in drug development could lead to blockbuster drugs, it is more probable that their integration in the drug development process will lead to drugs with smaller market potential. A fragmentation of the drug market is foreseeable in the upcoming genomic era but this fragmentation does not necessarily spell the end of economic investments or profitable drug development as some within the pharmaceutical industry might fear. A controlled fragmentation of the drug market could in fact be beneficial for the industry as it would enable better risk management in drug innovation by reducing the financial dangers associated with drug development. However, in order for pharmacogenomics to be considered financially beneficial, its integration in the drug development process will need to lead to sustainable drug development. A sustainable drug should be produced with the optic of responding not only to immediate needs but also to long term demands [Anonymous, 2007]. The promise of pharmacogenomics to achieve sustainable medicines that display a lower risk of
toxicity and therapeutic failures should be balanced, however, against the substantial difficulties in conducting large scale prospective clinical studies necessary to develop pharmacogenomic guided treatment guidelines and science policy [Ozdemir V. et al. 2007].

While one may question whether firms should have social responsibilities beyond maximization of profits, those within the business ethics community suggest that firms do have social responsibilities that reach beyond mere adherence to laws and regulatory policies [Heath, J. 2006]. In particular, there is a need for the industry to identify both the present and future healthcare needs of the population in a more global manner. Increased public awareness towards social and global justice issues are reshaping many industrial market realities and has led to emerging economic alternatives, such as organic foods, hybrid cars and generic drugs. If the pharmaceutical industry is to continue to thrive in the long run and respond to market pressures, it needs to acknowledge this new market reality. Opting for a more responsible market that acknowledges global public demand/needs and provides value for money to the public should help sustain the industry. Ultimately, the definition of ‘success’ for the pharmaceutical and biotechnology industries should take into account not only the more immediate goal of bringing safe and efficacious drugs into the market rapidly, but also keeping the pharmaceutical and health products in the market in a long term sustainable manner. A successful marriage between such short (time to market entry) and long term (sustainable products) metrics would eventually create a win-win situation for both investors in the industry and patients who are in need of high quality pharmaceuticals.

In this paper, we have proposed various ways that the drug development process could adapt to become more socially responsible. These different strategies can be summarized as promoting a drug development model focussed on sustainability – instead of the old blockbuster model – that incorporates both financial and social requirements and pays attention to the complex network of interactions between the two. We suggest that adopting a responsible drug market strategy could provide grounds for greater benefit for all. Pharmacogenomics also demands a more inclusive scientific model of drug development and commercialization whereby global health needs and hitherto disenfranchised interdisciplinary professional analytical frameworks – including those developed by social scientists and bioethicists – are taken into account as pharmacogenomics transitions from molecular discoveries to concrete applications at point of patient care.

In conclusion, we argue that the blockbuster market model for drug development, as it currently stands, is no longer tenable and propose that pharmacogenomics considerations be included in the drug development process to ensure market diversification, risk management, and social responsibility. A socially responsible drug development that addresses inequities in patient care and international health should acknowledge the new global reality and re-orient drug development models towards more targeted personalized medicines. This would meaningfully contribute to the customization of drugs to individuals while also potentially helping reduce global disparities in access to health care.

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DUALITY/CONFLICTS OF INTERESTS

None declared.

ABBREVIATIONS

FDA = US Food and Drug Administration
HIV = Human Immunodeficiency Virus
NDA = New Drug Application
NME = New Molecular Entity
R&D = Research and Development

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