



Personalized medicine: using effective partnering for managing the risk of legal liability

Mollie Roth

Corporate Counsel, VP,
Business Development
Tel.: +1 202 657 6518;
+1 202 280 5887;
E-mail: mollie.roth@
diaceutics.com

Beyond the economic cost–benefit analysis of incorporating pharmacogenomics into the process of drug development, it is time for the players in the industry to begin considering the long-term potential legal liabilities that may arise, and to undertake a legal analysis to identify and avoid those risks to the greatest possible extent. The current economic model being considered for pharmacogenomics technologies fails to take this legal risk into consideration, and therefore does not provide a complete picture of the incentives and disincentives of entering into this space. However, the more evenly weighted balance of all of the economic interests – costs, benefits and risks – can be tipped into the positive through effective partnering relationships between the pharmaceutical and diagnostic industries, and the diagnostic industry and pharmacy benefit managers. Such relationships will provide companies not only with needed economic incentives, but also with added protection from the potential future legal liabilities.

While there are compelling health benefits to be gained from the incorporation of pharmacogenomics (PGx) into the process of drug development, the current economic model and lack of government regulations do not provide the needed incentives and protections to drive players into the market. Furthermore, stakeholders are at present only considering the cost–benefit analysis of entering the market, which does not provide a true calculation of the likely rewards.

To that current paradigm, companies must also consider the potential for PGx to raise the risk of legal liability. While litigation directly addressing the legal standard to which a manufacturer will be held who uses PGx technologies in the drug-development process has not yet arisen, it is only a matter of time before it does. This is especially true if a patient suffers an adverse drug reaction (ADR) from the use of a drug that should have been contraindicated based on the patient's genotype, or a contraindication is present without the means to identify if the patient possesses the specific polymorphism at risk.

While the potential legal liabilities seemingly put any ultimate economic benefits of entering the market at risk, it is possible to create effective partnering relationships that will actually tip the balance of the calculation of these three variables – costs, benefits and risks – into the positive. These partnerships will accomplish that by driving down the costs of entering into the market and by providing management of

the potential litigation liabilities, ultimately making entering the personalized medicine market a more economically secure endeavor.

Background

Pharmacogenomics: hype versus hope

PGx is truly changing the entire landscape of both the pharmaceutical industry and the practice of medicine. However, the hype and hope surrounding personalized medicine has made this next logical step in scientific development something of a misnomer and has, to a certain extent, burdened it with unrealistic expectations. The practice of medicine has always been 'personal', with a doctor considering each individual patient's symptoms and disease state in light of family and personal history in combination with the most current state of medical knowledge. The 'revolution' that is the family of PGx studies – both the definition and understanding of the significance of genetic variations that govern individual responses to drugs as well as the ability to more accurately predict the future likelihood of contracting disease – is nothing more than a continuation of the scientific advances in therapeutic and diagnostic technologies of the last few decades.

PGx simply promises to continue that revolution on a level previously thought impossible – the genetic level. From a treatment approach, PGx uses biomarkers to identify the specific gene or genes responsible for variations in an individual's reaction to drugs. These biomarkers can speed the drug-development process and,

Keywords: big pharma, blockbuster model, companion diagnostic, cost–benefit analysis, design defect, diagnostic, duty to warn, economics, genes, genetic, legal liability, litigation, medical malpractice, personalized medicine, PGx, pharmaceutical manufacturer, pharmacogenomics, pharmacy benefit managers, physician, polymorphism, product liability, risk, stakeholders, third-party payers, FDA

future
medicine part of fsg

when they are incorporated into tests called companion diagnostics, to be administered to individual patients, will revolutionize prescribing decisions and how medicine is practised. From a preventative approach, PGx looks at mutations in genes implicated in certain types of diseases or protein expression, at present most typically in cancer, and uses that information to predict an individual's future likelihood of developing that disease.

Blockbuster model: prognosis?

Full recovery unlikely

The question, then, is not whether to utilize these new PGx technologies, but to identify the optimal methods for incorporating them to increase consumer health, while achieving the most advantageous economic benefit. Much thought and many articles have been devoted to what mechanism will ultimately drive the Personalized Medicine revolution, with everything from the failing state of the healthcare system to economics, litigation and third-party payers being cited as possibilities. Furthermore, the use of PGx technologies has itself been implicated as a possible cause in the downfall of the blockbuster model.

However, in reality, the mechanism that is driving the revolution is infinitely more organic. It is the critically ill condition of the blockbuster model of pharmaceutical development itself that is the inherent mechanism driving the paradigm shift. The industry has been aware of the decline in the blockbuster model for some time, and is now scrambling to cultivate and embrace a new development paradigm to replace the model on which it built its fortunes. PGx is not contributing to the downfall of the paradigm; rather, it is merely rushing to fill the vacuum being created as the blockbuster model continues to falter.

The factors that have afflicted the health of the blockbuster model are numerous, but most notable are the dwindling product pipelines failing to keep pace with the loss of patent protection and the increasing costs of developing drugs, neither of which are likely to experience a turnaround. It is estimated that development costs to bring a new drug from research idea to a US FDA-approved treatment are approximately US\$800 million [1]. Furthermore, only 9% of potential target compounds ever reach the stage of being included in a new drug application (NDA) to the FDA and, of potential drug candidates that gain approval in an NDA and advance to Phase I trials, only 21.5% are ever approved

for market [2]. Efficacy and safety issues alone, which may ultimately be better addressed through PGx, cause the failure of 58% of drugs during development [2].

The pharmaceutical industry has also taken note of the fact that, while it invests 94% of the industry-wide R&D, 70% of the drugs approved by the FDA come from the biotechnology market [3]. Further compounding the problem is the increasingly insistent push toward the use of generics by third-party payers. For the first time, in 2004, the number of prescriptions written for generics outnumbered the number of prescriptions written for name-brand drugs [3].

Finally, the ill-health of the blockbuster model is unlikely to improve because the industry has already addressed the basic problems of modern health for which pharmaceuticals (Rx) applicable to broad-based populations and thus able to drive billion-dollar sales figures are available. With the present need for therapies able to treat and provide relief from more complex, multifactorial problems increasing, the blockbuster model of Rx therapies safely applicable to broad segments of the population is simply no longer viable. The industry is now facing an increasing tide of complex, chronic problems that are endemic to an aging society – diseases such as high cholesterol, heart disease and diabetes – as well as other complex problems such as infertility and obesity. While the blockbuster model may never completely expire, as the recent runaway successes of sleep aids such as Ambien® and Lunesta™ have demonstrated, it is unlikely to be able to continue to support the industry on which it is based.

Present PGx economic model

Thus, PGx technologies are being seen as a way to revive the industry by decreasing development costs and providing better tailored therapies directed at patients for whom they will actually be efficacious. Pharmaceutical manufacturers are seeking the optimal means of incorporating PGx into the drug-development process and are looking for representative economic models that will predict the likelihood that the increased investment required today will translate into profits down the road. However, problematic is the fact that the economic analysis presently being undertaken is incomplete, thus providing a skewed picture of the balance of factors arising from incorporating PGx.

The present economic model typically only balances the costs of incorporating PGx technology against the potential benefits, thus providing an incomplete picture [4]. When considered in light of this simplified cost versus benefit analysis, incorporating PGx seems only to result in an evenly balanced economic scale, thereby providing the industry with little incentive to rapidly shift the paradigm. Furthermore, these variables are being weighted down by the industries greatest fear – that there is no possibility of sustaining the historic profit and growth picture of the industry with the use of PGx. This fear arises out of the notion that sales of a PGx product will only ever provide minimal return on an initially very high investment, and will never be able to supplant the blockbuster model (a billion dollars in sales) as it, by necessity, targets a smaller subpopulation of consumers. This, however, fails to consider the fact that approximately 50% of therapies prescribed today are actually ineffective, if not harmful, to patients taking them [5,101]. This lack of efficacy and prevalence of ADRs often results in a rapid decline in patient compliance rather than the long-term dosing necessary for optimal results. It is highly likely that the use of PGx technologies will result in near-equivalent revenues owing to increased patient compliance over greater time horizons, as they provide more efficacious results to a more targeted population.

Including legal risk in the economic analysis

There is, however, another variable which should be included in this economic modeling – the risk inherent in incorporating PGx into drug development, as it pertains to potential legal liabilities. As the pharmaceutical industry considers the potential, both good and bad, of incorporating PGx into the drug-development process, it must consider its present litigation pressures as well as the possibility for further risk arising from the use of PGx strategies.

In the past decade, the pharmaceutical industry has been plagued with a landslide of product liability litigation resulting from a number of factors, including the rise of state laws easing the way for class actions, and increased post-market ADRs leading to black-box warnings or recalls. Product-liability litigation currently costs the pharmaceutical industry billions of dollars per year, often representing upwards of ten-times any one individual company's research and development costs [102,103]. The

increased use of PGx technologies may well give rise to an initial further increase in the litigation the industry faces.

Costs of litigation: direct & indirect

The direct costs from these litigations are readily calculable and include the actual defense costs as well as eventual settlements or verdicts, decreased profits from reduced drug sales or a complete recall and reduced shareholder confidence resulting in depressed stock prices. However, it is the indirect, but very equally real costs of adverse media coverage that are more damaging to the industry as a whole. While the dollar costs relating to such coverage may be impossible to quantify, they are immediately obvious based on the volume of negative media articles painting the industry as 'Big Pharma' – corporations that put profits ahead of consumers and the bottom line ahead of patient safety [104–107]. A 2005 survey demonstrated that a half of adults have unfavorable opinions of pharmaceutical companies, ranking them ahead of oil and tobacco companies in favorability, but behind many other groups such as hospitals, airlines and banks [107].

The risks and pressures being brought to bear on the industry are only likely to increase as consumers become increasingly aware of their treatment options and continue to have an increased stake in their healthcare decisions. With the rise of directed media outlets and increased internet access, consumers are becoming better informed and seeking out greater amounts of information regarding their health and treatment options than ever before. At present, approximately 95 million Americans, or 79% of all internet users, regularly research information relating to their health online [6]. The use of PGx, a technology most consumers do not comprehend, and of which many are afraid, will only escalate this trend.

It is very likely that the pharmaceutical industry and treating physicians will eventually face legal liability arising from the use of PGx in drug development. As described more fully below, this liability will likely arise in the form of standard product liability litigation, medical malpractice actions and novel design defect theories. If sufficient time passes, liability may even arise from failing to utilize PGx strategies in drug development as the state of the art shifts.

Therefore, it is absolutely imperative that stakeholders not only consider the cost-benefit analysis of incorporating PGx, but also calculate the risk of entering this space. Only by considering all three

of these variables will the industry obtain a truly representative calculation of the realities of entering the PGx space. This calculation will provide stakeholders with the ability to identify and incorporate appropriate means of risk management sufficiently early in the process – such as creating and entering into effective partnerships designed to share the risk – to allow them to realize the full economic benefits of using PGx strategies.

Potential legal liabilities

Avoidance of PGx: short-term protection, long-term loss

Before we consider the potential legal liabilities of entering the Personalized Medicine space, we should consider the possible liabilities of not entering the space. Some companies, considering the cost–benefit analysis of incorporating PGx strategies into the drug-development process, may decide that the costs are not outweighed by the benefits, in spite of the ill health of the blockbuster model. Such companies may allow their competitors to forge ahead, test the waters and design the optimal methods for incorporating PGx strategies, with the intent to follow in their footsteps and learn from their successes and failures. It would appear that an added bonus of doing so would be to avoid any potential legal liabilities by simply ‘opting out’ of the present need to use PGx and continuing to follow the old paradigm.

There is, however, a finite limit on the time period that this strategy will afford any protection as the state of the art continues to move toward the use of genomic data in drug development. There has been a significant increase in PGx information included in labels over the past decade, and approximately 10% of all labels for currently approved drugs already contain PGx information [108]. Furthermore, the FDA is currently reviewing postmarketing surveillance data on a number of drugs, and has already asked manufacturers to retroactively create companion diagnostics where a genetic component to the ADR is apparent. This retroactive ‘fix’ may well become the basis for litigation, alleging that the manufacturers should have:

- Used PGx technologies in designing the drug
- At minimum, brought the drug to market with a warning
- Provided the necessary companion diagnostic to identify the specific polymorphism

Manufacturers choosing to opt out may only be delaying the inevitable and find themselves sitting back on their heels if the courts find

that the state of the art has changed more rapidly than they anticipated. For a time, manufacturers may be able to avail themselves of the ‘state of art’ defense with respect to design defect claims, which only holds them accountable for those things that are ‘reasonably scientifically knowable at the time of manufacture’. This defense, however, is limited to design defect claims and is unlikely to provide safety in a failure to warn claim.

Manufacturers considering both the cost–benefit analysis, as well as the risks and how to properly mitigate them, will anticipate potential legal liabilities and undertake steps to incorporate PGx throughout the lifecycle of drug development. Much is to be gained from the use of PGx strategies if incorporated through the lifecycle of the drug. By utilizing biomarkers to streamline clinical trials and bringing the drug to market with a specific warning and a companion diagnostic, forward thinking manufacturers will be ahead of the need for FDA-requested retrofits, potentially avoid some of the legal liabilities and realize a positive gain on their investment.

Legal basis of liability

There are risks inherent in the use of all pharmaceuticals. The law balances the inherent risks of a drug against its utility to determine whether the dangers are outweighed by the benefits and whether the drug should be allowed to stay on the market [7]. Unfortunately, the public to whom these drugs are prescribed are typically unaware of this risk–benefit analysis, believing instead that pharmaceutical products, when FDA approved, are completely safe. When these expectations are inevitably not met, such as when postmarket surveillance begins to reveal ADRs that failed to present in smaller clinical trial groups, public confidence falters in both the industry and the government agency tasked with regulating the industry – the FDA.

The inevitable consequence is litigation that seeks to recompense both the consumer’s injuries and to punish the industry for actions undertaken without malice or intent to harm. The legal liability that will follow from the use of PGx strategies will most likely center on failure to warn claims, although some novel arguments may also be put forth and tested. The severity of the risk depends largely on the steps that manufacturers undertake in incorporating PGx strategies and whether they implement those strategies throughout the drug-development lifecycle, or

only in part. The relative degree of risk, therefore, is a continuum depending on whether manufacturers use long-term, forward thinking strategies or simply seek to utilize PGx on an *ad hoc* basis. The relative degree of risk will depend upon a number of factors, including: whether PGx strategies are used solely in the development process; are used to exclude participation from clinical trials based on specific polymorphisms; whether there are warnings included in the label and if these are general or specific to the polymorphism at risk; and whether or not means are provided to identify whether individuals carry that polymorphism.

The differing strategies that stakeholders may use in incorporating PGx strategies, and the potential legal claims that may flow from those decisions, are discussed below.

Product liability: failure to warn

As noted above, certain products are considered inherently dangerous, but have sufficient utility that the danger is not considered unreasonable, nor does it make the product defective. Pharmaceuticals are included in the list of items that are considered inherently dangerous, but have sufficient utility that their dangers are outweighed [7].

The inherent risks of pharmaceuticals are further mitigated by the use of warnings directed to the intended users of the product. Thus, a drug manufacturer has a duty to warn potential users, through the ‘learned intermediary’ or prescribing physician, of any reasonably known or knowable risks or dangers of the use of its manufactured drug [8]. Liability for failure to provide an adequate warning, which can be demonstrated by showing either a complete absence of a warning or that the warning provided was inadequate, is typically only imposed when the manufacturer has actual or constructive knowledge of the risks inherent in using the product. However, the use of PGx technologies in the drug-development process shifts back in time when such knowledge may be deemed to have arisen on the part of the manufacturer.

Stratification of clinical trials

One of the great promises of PGx is the ability to speed the drug-development process, making it more economical and enabling companies to get drugs to the market faster than is currently possible. As noted above, it presently costs approximately US\$800 million to bring a drug from research idea to an FDA-approved treatment. In addition, it also typically takes 7–12 years to

complete the full phase of animal and human clinical trials required by the FDA and, on average, an additional 12 months for the drug to be approved once the NDA is submitted to the FDA [109].

Of those obligations, the clinical trials fully represent 20% of the overall costs in the drug-development process. PGx strategies can radically reduce those costs by using genetic biomarkers and companion diagnostics to reduce the size of the trials, thereby making them smaller, faster and far more economical [9]. As noted by the CEO of one pharmaceutical company [4,10]:

“Biomarkers and PGx will help us target better the patients who will participate in clinical trials, so instead of a shotgun approach, as we do today – having a large population with a given disease – we would test it on a much smaller population.”

Clinical-trial participants are already stratified based on certain parameters – age, disease and other comorbidities – by which they are included in, or excluded from, participation. Historically, researchers have discovered adverse reactions likely to occur through the use of a drug only as a concomitant to testing for safety and efficacy once the clinical trials have started. Furthermore, many ADRs do not arise until postmarket and have been used by a much broader and less well-defined group of patients.

However, PGx technologies provide drug manufacturers with a much more precise means to identify potential ADRs before testing in humans and to potentially streamline the clinical trials [11]. Through the use of genetic biomarkers and companion diagnostics, researchers are now able to better understand individual differences in an individual’s ability to metabolize and tolerate drugs. By genotyping participants during the early stages of clinical trials, researchers are able to include in later trials only those likely to benefit from the drug and, more importantly, to exclude those likely to experience ADRs [9]. Biomarkers may now be used at the clinical-trial phase as one more parameter to separate participants into significantly more distinct groups – those likely to benefit from the drug; those likely to experience no reaction, positive or negative; and those likely to experience adverse events. This new technology, therefore, will allow researchers to run smaller, faster trials that provide greater evidence of the drug’s efficacy, with probable evidence of fewer side effects.

Duty to warn: arising earlier

While the use of PGx technologies will significantly reduce the costs of drug development through a reduction in clinical-trial scope, they also provide manufacturers with concrete, absolute data about exactly which individuals are likely to be injured by use of a drug. Through this new technology, knowledge on the manufacturer's part can be said to arise much earlier in the drug-approval process than under the current paradigm. This newfound ability to identify specific causation of harm before it occurs in the clinical trials or in the general populace results in a shifting back in time of the moment when constructive knowledge may be deemed to have arisen on the part of drug manufacturers [12].

Thus, because a manufacturer has a duty to warn potential users of any reasonably known or knowable risks of the use of their drug, the use of companion diagnostics to stratify clinical trials would arguably give rise to a duty earlier in the development process to warn those individuals possessing the specific polymorphism that gives rise to the ADR or lack of efficacy. Although it is a widely accepted fact that more than 50% of the drugs prescribed today prove ineffective for the individuals taking them, to date, drug manufacturers have had no ready means to precisely identify such individuals. It is a vastly different issue, however, when the manufacturer has the means to identify those individuals back at the clinical-trial stage.

Based on this use of PGx, an individual who carries a polymorphism of the type that was excluded from the clinical trials could sue a drug manufacturer, alleging that it breached its duty to warn by marketing a drug for widespread use knowing, based on the manufacturers stratification of the clinical trials, that the drug was ineffective or harmful to a certain cohort.

Duty to warn: heavier burden

The ability to identify specific causation of harm before it occurs in the clinical trials or in the general populace not only shifts back in time when constructive knowledge may be deemed to have arisen on the part of drug manufacturers, but it may well also increase the burden for a more specific or targeted warning than is required at present.

The generalized warnings currently used in drug labels may no longer be deemed sufficient when PGx technologies have been used to identify and exclude individuals with specific polymorphisms. Courts considering the warnings included for drugs manufactured in this manner

may well find them inadequate without information regarding the specific polymorphisms at danger of ADRs from the use of the drug.

Possible legal defenses

A manufacturer may have several defenses that it could put forth in this situation. However, the possibility of these arguments proving effective or providing a complete defense is unlikely, given the explicit evidence of the potential for harm for a specific polymorphism utilized at the clinical-trial stage.

A manufacturer could argue that a warning, even a specific one, would have been meaningless without the means to identify if the individual carried the specific polymorphism [13]. This is a weak defense that is infrequently successful and could ultimately prove to undercut a manufacturer's ability to utilize PGx on an *ad hoc* basis. It would do so by lending support to the novel argument, discussed below, that drugs designed in this manner are defectively designed because they fail to provide the means to assess the risk–benefit profile of using the drug without a companion diagnostic.

Validation would be another possible defense available to a manufacturer, who could argue that the degree of evidence linking a particular genotype to an increased risk of an ADR was not sufficiently clear to merit a warning [13]. However, it is highly unlikely that a manufacturer would be allowed to have its cake and eat it too, as it were. If the evidence of possible ADRs was sufficiently valid to exclude individuals from participating in the clinical trials, it is unlikely that a manufacturer would be able to sustain a defense that a label warning was not merited.

In an effort to embrace every protection afforded them, manufacturers will also want to not shy away from including warnings about specific polymorphisms in the drug label. Manufacturers of drugs for which clinical trials have been stratified in this manner must give due consideration to labels submitted to the FDA for review, including information and warnings concerning the specific polymorphisms excluded from the clinical trials. Regardless of whether the FDA ultimately deems such warnings to be necessary, the prudent manufacturer will include them in its initial submission to better position its defense posture relating to possible future failure-to-warn claims. While there may or may not be a common-law duty to actually use this new technology, once a manufacturer decides to use it, particularly when it does so to stratify patient populations in

clinical trials, the duty to warn will be affirmatively created, and properly worded labels will provide some protection [14]. However, even with a specific warning in place, a drug manufacturer may still incur some risk where it fails to provide the means to identify the individuals possessing the specific polymorphism.

Warning without diagnostic: design defect claims

Based on the foregoing discussion, manufacturers may therefore consider incorporating PGx strategies more fully into the drug-development process and, where individuals are excluded from clinical trials based on a specific polymorphism, include a warning about the specific polymorphism in the label. In this way, the manufacturer will avoid standard product liability arguments and failure to warn claims.

Unfortunately, even undertaking this next step in the process may leave the manufacturer open to potential legal liability if the drug is brought to market without a companion diagnostic. As discussed above, a warning without the means to identify whether the patient has the specific polymorphism at issue, is in reality a meaningless warning. Although it is unclear at this point in time whether a court would find for or against a manufacturer, before any such claims have been brought, it is still a potential danger.

Furthermore, an individual who carries the genetic polymorphism that carries an increased risk of experiencing an ADR from the use of the drug could bring a lawsuit alleging that the drug is defective as designed, because it does not provide the means to test for the polymorphism. Such a claim alleges that the product that caused the injury was ‘defective’ and unreasonably dangerous. Pharmaceuticals have historically been held to a less strict standard for design defect, in recognition of the fact that manufacturers are unable to control the interaction of the drug in the body, which may cause harm. This lesser standard is reflected in the Restatement (Second) of Torts, still in place in many US states, which states that a manufacturer is not liable for design defect if the drug’s benefits exceed its risks. To date, the entire premise of the drug-development and approval process has been a balancing of the benefits against the risks in which certain risks, the adverse side effects, are deemed acceptable depending on the degree of benefit of the drug.

Furthermore, there is a new standard for pharmaceutical design defect claims which, while not yet adopted by every state, has been

suggested by some commentators to provide greater protection from design defect claims [13]. The Restatement (Third) of Torts states that a design defect claim can only be brought if a reasonable healthcare provider, balancing the foreseeable risks against the therapeutic benefits, would not prescribe the drug ‘for any class of patients.’ [15]. At first glance, it would appear that this would provide greater protection, allowing a manufacturer to argue that since the drug was safe for some patients, those without the polymorphism, it was not defectively designed [13].

However, without the means to identify who amongst a group of patients possesses the specific polymorphism, there is no way to balance the risk:benefit ratio of such a drug to identify any class of patients. An individual could bring a claim against the manufacturer alleging the drug was defectively designed, not because it caused ADRs amongst certain populations, those with the specific polymorphism, but because there was no way to identify whether someone was in that group of patients in advance of prescribing the drug. Thus, without the means to avoid prescribing the drug to an individual likely to be injured, the drug potentially becomes inappropriate for all classes of patients.

Possible legal defenses

In this situation, a manufacturer may be able to rely on the ‘learned intermediary’ defense, arguing that it discharged its duty to patients by providing warnings to the prescribing physicians [16]. The justification for the learned intermediary defense is grounded in the fact that consumers cannot buy prescription drugs directly [17]. Rather, they must first consult with and receive the approval of a physician. Therefore, by providing adequate warnings to a prescribing physician, who in turn provides appropriate patient-specific warnings, the manufacturer discharges its duty.

While the learned intermediary defense has proven useful in product liability actions to date, there are significant problems with using it in this context. In the situation described above, while the manufacturers have provided a warning to the treating physician, it is relatively meaningless without the means to identify individuals with the specific polymorphism.

Regardless of the relative strength or weakness of this defense, manufacturers have another issue in this context, which merits even greater consideration.

Best defense: effective partnerships

A manufacturer's best defense against such future possible legal liabilities is not to avoid them, but to become fully aware of them now and to undertake the most effective strategies to protect themselves against such future risks. The best way to limit the potential legal liability stemming from the use of PGx technologies in the drug-development process is very straightforward – manufacturers should bring that drug to market concurrently with the necessary companion diagnostic. While this could be done by the drug manufacturer itself, synergistic business partnerships with diagnostic (Dx) companies hoping to capitalize on the future of PGx technologies provide a much more potent and profitable partnership opportunity.

Although both the pharmaceutical and Dx industries have historically traveled on parallel paths, bringing those paths on convergent courses will provide great benefits for both industries in this instance. Working in tandem with the Dx industry will provide pharmaceutical manufacturers a partner better versed in the intricacies and development of Dx tests and better able to provide needed guidance on such aspects. More importantly, such partnerships will provide an additional layer of protection to the pharmaceutical industry from potential future legal liability. By working with the Dx industry as early in the process as possible, pharmaceutical manufacturers will be creating concrete evidence of their awareness of their potentially increased duty to warn and, if such partnerships are forged sufficiently early in time, will capture the shift back in time of when their duty to warn arises as a result of their use of PGx technologies.

Furthermore, as part of the cost–benefit analysis discussed above, partnerships between pharmaceutical manufacturers and the Dx industry represent a further possibility for manufacturers to outsource some or all of their R&D requirements and further reduce the costs of entering into the PGx space. Diagnostic companies recognizing this potential and coming to the table as going concerns seeking out appropriate partnering opportunities with drug manufacturers have the opportunity to provide tremendous support to the industry.

On the other side of this partnership, the shift in the drug-development paradigm presents the Dx industry with the opportunity to elevate itself from a marginal player in the therapeutic spectrum to become a true partner in this new

PGx venture. Historically, the Dx industry has emphasized a high-volume, low-cost business model that has limited its ability to truly expand into and capitalize on the healthcare space. Key stakeholders in the Dx space have the ability to capitalize on the risks of legal liability to the pharmaceutical manufacturers to alter that dynamic and to position themselves as necessary players by providing risk-management strategies.

Furthermore, the Dx industry will be able to link its products to the very powerful and effective pharmaceutical industry and avail itself of their skills and abilities. By partnering with large pharmaceutical manufacturers with established clinician networks and sales teams, the Dx industry can leverage that economy of scale to realize far greater return on investment than is possible as a stand-alone Dx company. Furthermore, as consideration is being given to the outdated diagnostic reimbursement scheme in the USA, the Dx companies would be wise to align themselves with a more influential side of the industry better able to encourage changes in that scheme. In doing so, the Dx industry will thereby alter the historic dynamic between the two industries and redefine their role in this new venture moving forward.

Working together to design and market a linked therapy and companion Dx, the two industries will thus be able to provide both guidance, increased market capitalization and protection to one another. Such a convergence of compatible but separate industries is not a case of first impression and will serve as the new working model moving forward. New and innovative partnership agreements will need to be crafted that consider and incorporate both the potential for increased risk and appropriate allocation of profit based on the strengths and protections that each side brings to the venture.

The combined impact of reducing the costs of entering the PGx space and providing management of possible legal liabilities will ultimately tip the presently level cost–benefit balance into the positive as the risks, or future legal liabilities that manufacturers face from not having a companion diagnostic, are reduced. Thus, the economic model, now fully developed to encompass not simply the immediate cost–benefit scale of entering the space, but also considering the future risks, truly demonstrates the potential return on investment to be gained by utilizing PGx technologies in the drug-development process. That return is very definitely tipping the scales into the positive.

Other unique opportunities beyond the pharmaceutical manufacturer and Dx industry model may well present themselves as companies that orbit the industry become more aware of how it may be to their benefit to become involved. Pharmacy benefit managers, for example, have a business model wholly focused on the provision and management of pharmaceutical products coupled with vast amounts of historical data standing ready to be mined for potential patterns of ADRs and retrospective studies that could be used to gain approval for new companion Dx tests. These companies have the potential to become involved in the PGx process either by providing partnering opportunities to the Dx industry to provide needed data for clinical approval, or by potentially creating their own in-house Dx capabilities and partnering directly with the pharmaceutical industry. This may well provide a pharmacy benefit manager with a revised business model that will allow them the opportunity to increase their return on investment while providing the means to control the costs within their own patient populations, thereby enabling them to capture both the savings and profits from doing so.

Conclusion

PGx promises to provide a new drug-development paradigm that will augment, if not ultimately replace, the traditional blockbuster model that has been in ill health for some years. Just like the risks that the industry currently faces in the traditional drug-development paradigm from product liability litigation and failure-to-warn claims, incorporating PGx strategies into the drug-development process also carries potential legal liabilities.

Current economic models under consideration are incomplete, however, thus providing a skewed picture of the gains to be achieved through the use of PGx strategies. Sole consideration of the cost-benefit analysis tends to indicate a clear lack of viable economic incentives to encourage key stakeholders into this market. However, with the added consideration of the potential legal risks, and the means to mitigate those risks for the benefit of both the diagnostic and pharmaceutical industry, the balance of factors clearly tips in favor of the use of PGx. Thus, the economic model, now fully developed to encompass not simply the immediate cost-benefit scale of entering the market, but also to consider the future risks, truly demonstrates the potential return on investment.

In order to capitalize on these potentials, effective partnering between the pharmaceutical and diagnostics industries should be considered and encouraged. The diagnostics industry has the opportunity to elevate itself from being a marginal player in the therapeutic spectrum, emphasizing a high-volume and low-cost business model, to become a true partner in this new PGx venture. Key stakeholders in the diagnostics space have the ability to capitalize on the risks of legal liability to the therapeutic manufacturers to provide needed protection and thereby alter the dynamic moving forward.

Furthermore, beyond the pharmaceutical and Dx industries, PGx technologies may well provide the perceptive pharmacy benefit management companies with the means to contain their spiraling costs, capture profits from PGx technologies and create an entirely new set of industry partnerships.

For those pharmaceutical manufacturers preferring to go it alone, consideration of the impacts and effects of incorporating PGx strategies into the drug-development paradigm must be undertaken throughout the lifecycle of drug development in order to best protect themselves from legal liabilities. The best way to limit this legal liability would be for the manufacturer of a drug where PGx strategies have been used to streamline and reduce the costs of R&D to bring that drug to market concurrently with the necessary companion diagnostic. Only by incorporating these strategies from conception to market will pharmaceutical manufacturers afford themselves any level of protection from the potential legal risks.

Future perspective

In the next 5–10 years, we will continue to see a slow and steady increase in manufacturers launching therapies developed with PGx technologies for targeted populations. In the immediate future, we will likely see an increase in cross-industry conversations about the most effective methods for doing so and, hopefully, an increasingly collaborative atmosphere between the pharmaceutical industry and the diagnostic industry. We may well also see some unexpected relationships between the pharmaceutical industry and pharmacy benefit managers and/or third-party payers, as those entities begin to truly understand the advantages of PGx technologies for their business models.

Of necessity, the pharmaceutical industry will also continue to reach out to the FDA to consider and try to craft an appropriate regulatory

framework for these new technologies. Furthermore, we may well see the beginnings of movement in the Centers for Medicare & Medicaid Services (CMS) reimbursement scheme to better reflect and compensate the newer state of the art in diagnostics.

As more and varied targeted therapies are launched, we are likely to see the beginnings of legal actions testing the boundaries of liability for failure to warn, design defect, genetic privacy and off-label issues. As industry becomes more comfortable with the use of PGx strategies, and as legal actions potentially begin to arise, the industries'

focus will shift from present short-term legal problems (intellectual property and licensing) to the longer-range legal liability issues discussed here. Companies will increasingly incorporate Legal Risk Reviews into the planning process for targeted therapies to ensure they are considering and mitigating all potential legal risks at an appropriately early point in the process.

Acknowledgement

The author would like to thank the products liability group at the law firm of Nixon Peabody LLP for the generous amount of time it allowed for this endeavor.

Executive summary

- The compelling health benefits to be gained from the incorporation of pharmacogenomics into the drug-development process may not be realized because the current cost-benefit economic model does not provide a true calculation of the likely rewards of doing so.
- The critically ill condition of the old model of pharmaceutical development, the blockbuster model, is the inherent mechanism that is driving the paradigm shift to pharmacogenomics.
- Companies must consider the potential for pharmacogenomics to raise the risk of legal liability, especially if a patient suffers an adverse drug reaction from the use of a drug that should have been contraindicated based on the patient's genotype.
- While the potential legal liabilities seemingly put any ultimate economic benefits of entering the space at risk, it is possible to create partnering relationships that will actually tip the balance of the calculation of these three variables – costs, benefits and risks – into the positive.
- Avoiding the use of pharmacogenomics strategies will only provide limited protection as the state-of-the-art moves towards incorporation of these technologies.
- The use of pharmacogenomics should be undertaken throughout the lifecycle of drug development to reduce the legal risks, and not simply be used to reduce R&D costs.
- Using pharmacogenomic strategies in discrete segments of the drug-development process may lead to failure-to-warn claims and heavier burdens where clinical trials are stratified but the drug is not brought to market with a warning or contains a warning without the means to identify individuals with the specific polymorphism at risk.
- There are a number of possible defenses available to the drug manufacturer, but none are likely to offer a complete defense.
- The best defense is to utilize effective partnering opportunities with the diagnostic industry to ensure that pharmacogenomics strategies are incorporated throughout the lifecycle of a drug.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Frank R: New estimates of drug development costs. *J. Health Econ.* 22, 325–330 (2003).
 2. *Personalized Medicine: The Emerging Pharmacogenomics Revolution.* PriceWaterhouseCoopers, Global Technology Centre, Health Research Institute, 7 (2005).
 3. *At Sea, Forecast 2007.* Pharmaceutical Executive, 50 (2007).
 4. Keeling P: Personalized medicine: the absence of 'model-changing' financial incentives. *Personalized Medicine* 4(1), 73–81 (2007).
 5. Ridge J: Reimbursement and coverage challenges associated with bringing emerging molecular diagnostics into the personalized medicine paradigm. *Personalized Medicine* 3(3), 345–348 (2006).
 6. Fox S: *Health Information Online.* Pew Internet & American Life Project, Washington, DC, USA (2005).
 7. Restatement (Third) of Torts: Products Liability, § 6, Comment b, "The traditional refusal by courts to impose tort liability for defective designs of prescription drugs and medical devices is based on the fact that a prescription drug or medical device entails a unique set of risks and benefits. What may be harmful to one patient may be beneficial to another."
 8. Restatement (Second) of Torts: "In the pharmaceutical context, a manufacturer's duty to warn may be discharged by providing warnings to the physician, not the actual end-user of the product. This is based on the rationale that the physician acts as a "learned intermediary" between the manufacturer and the consumer and is best able to undertake the cost/benefit analysis to determine the appropriateness of the specific drug for the specific patient and disease."
 9. Roses AD: Pharmacogenomics and the practice of medicine. *Nature* 405, 857–865 (2000).
- Discusses that the early ability to accurately identify individuals likely to experience adverse drug reactions makes it

- incumbent upon researchers that such individuals be excluded because, in conducting clinical trials, as in the practice of medicine, a physician is required to ‘do no harm’.
10. Carlson B: Diagnostic assays a key to personalized medicine. *Biotech. Healthcare* 15–18 (2006).
 11. *Personalized Medicine: The Emerging Pharmacogenomics Revolution*. PriceWaterhouseCoopers, Global Technology Centre, Health Research Institute 12–14 (2005).
 12. Thomas PR: Twenty-first century toxicogenomics meets twentieth century mass tort precedent: is there a duty to warn of a hypothetical harm to an “eggshell” gene? *Washburn Law J.* 42, 547–574 (2003).
 - **Argues that the use of these type of diagnostics will pose significant liability issues based on a theory of genotoxic harm for manufacturers of genotoxic compounds and radiation sources.**
 13. Marchant G, Milligan R, Wilhelmi B: Legal pressures and incentives for personalized medicine. *Personalized Medicine* 3(4), 391–397 (2006).
 14. Urquhart JE, Adams CK, de Santos LE: The duty to use pharmacogenetics and pharmacogenomics to reduce the risk of idiosyncratic drug-induced liver injury. *Drug Recall Litigation Report* (2004).
 15. Restatement (Third) of Torts: American Law Institute, Products Liability.
 16. Restatement (Third) of Torts: Products Liability, § 6, Comment d, reporters’ note (1997).
 17. Seib KE Jr, Miller AE: Courts should rebuff assault on ‘learned intermediary’ rule. *Andrews Pharmaceutical Litigation Reporter* (1997).
- Websites**
101. Alliance for Human Research Protection, citing Dr Allen Roses, then worldwide vice-president for genetics at GlaxoSmithKline www.ahrp.org/infomail/03/12/08.php
 102. Trial Lawyers, Inc.: Health Care, Manhattan Institute, Center for Legal Policy. Merck’s 2004 research and development expenditures were US\$4.01 billion, based on the company’s 2004 annual report www.merck.com/finance/annualreport/ar2004/home/
 103. Wyeth’s 2004 research and development expenditures were US\$2.46 billion, based on the company’s 2004 annual report <http://library.corporate-ir.net/library/78/781/78193/items/141903/AR04.pdf>.
 104. Big Pharma, Bad Science, The Nation www.thenation.com/doc/20020805/newman20020725
 105. Big Change No Challenge for Big Pharma, Fortune, March 6, 2007, Big Tobacco and Big Pharma: same tactics, different chemicals www.newstarget.com/008291.html
 106. CNN Money http://money.cnn.com/2007/03/06/news/economy/pluggedin_simons_pharma.fortune/index.htm
 107. The Henry J Kaiser Family Foundation, HealthPoll Report (Jan/Feb 2005) www.kff.org/healthpollreport/feb_2005/
 108. Table of valid genomic biomarkers in the context of approved drug labels, US FDA Center for Drug Evaluation and Research www.fda.gov/cder/genomics/genomic_biomarkers_table.htm
 109. FDA’s drug review and approval times, US FDA, Center for Drug Evaluation and Research www.fda.gov/cder/reports/reviewtimes/default.htm.