PERSPECTIVES

OPINION

Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective

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Abstract | Pharmacogenomics and pharmacogenetics provide methodologies that can lead to DNA-based tests to improve drug selection, identify optimal dosing, maximize drug efficacy or minimize the risk of toxicity. Rapid advances in basic research have identified many opportunities for the development of 'personalized' treatments for individuals and/or subsets of patients defined by genetic and/or genomic tests. However, the integration of these tests into routine clinical practice remains a major multidisciplinary challenge, and even for well-established biomarkers there has been little progress. Here, we consider this challenge from a regulatory perspective, highlighting recent initiatives from the FDA that aim to facilitate the integration of pharmacogenetics and pharmacogenomics into drug development and clinical practice.

The promise of pharmacogenomics (PGx) lies in its potential to identify sources of inter-individual variability in drug response that affect drug efficacy and drug safety. The identification of PGx BIOMARKERS (see Glossary) can lead to the development of PGx tests that can be used to individualize therapy with the intent of maximizing effectiveness, minimizing risks and optimizing doses in therapeutic applications.

In this article, our definition of PGx is very broad, and includes the study of inter-individual variations in whole-genome or candidate gene SINGLE-NUCLEOTIDE POLYMORPHISM (SNP) MAPS, HAPLOTYPE markers and alterations in gene expression or inactivation that might be correlated with pharmacological function and therapeutic response. Pharmacogenetics (PGt), by contrast, is narrower in definition and refers to the study of inter-individual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics), including polymorphic variation in genes that encode transporters, drug-metabolizing enzymes, receptors and other proteins. We will not consider proteomics in this article, although gene-driven proteomic patterns in serum ('protein signatures') show promise, for example, as prognostic or screening biomarkers for staging cancer or for identifying high-risk subgroups in a disease population. We acknowledge that there is overlap between the definitions of PGx and PGt, and we will use the terms 'pharmacogenomic test' or 'pharmacogenetic test' to refer to an assay to study these inter-individual variations in conjunction with drug therapy.

Translating PGx from bench to bedside (or from discovery to marketability) is a multidisciplinary problem that involves addressing philosophical, societal, cultural, behavioural and educational differences between the private and public sector, as well as issues unique to drug development, extent of scientific expertise, interdisciplinary communication and clinical practice. However, we will focus on a regulatory science perspective of PGx and PGt that will cover three broad areas: first, the views of the Food and Drug Administration regarding the value and challenges of integrating PGx and PGt into the continuum of drug research and development and regulatory decision making; second, the major, structured approach that the FDA has undertaken to encourage the use of PGx and PGt both in drug development and clinical practice; and third, selected examples of how PGx and PGt have been used both in new drug development and in updating the labels of approved drugs. Within the context of these three areas, we will point out various challenges that drug developers, regulatory agencies, health-care providers and others will have to address in order to attain the benefits of PGx and PGt more fully.

Drug R&D: what is the problem?

By and large, drug development and private- and public-sector research has been reasonably successful during the past 15–20 years, and there is, in fact, much to celebrate. However, as indicated by analysis and metrics provided by regulatory agencies in the United States and Europe, we are now facing a major challenge: it is essential to improve the success of pharmaceutical research and development (R&D). Although the productivity of drug discovery and early development has increased over the years (as measured by the upward trend in the identification of new molecules, drug targets and INVESTIGATIONAL NEW DRUG APPLICATIONS (INDs) filed with the FDA), the number of major drug and biological product NEW DRUG APPLICATIONS (NDAs) and BIOLOGIC LICENSE APPLICATIONS (BLAs) for new molecular entities that have been submitted to the FDA has steadily decreased during this period. The pharmaceutical industry submitted almost 50% fewer applications to the FDA in 2002–2003 than it did in 1996–1997 (FIG. 1). During the same timeframe, investment in biomedical research spending for the private and public sectors increased almost 2.5-fold (FIG. 2). So, it is clear that many biomedical discoveries have not been transformed into marketable products in the United States and worldwide.

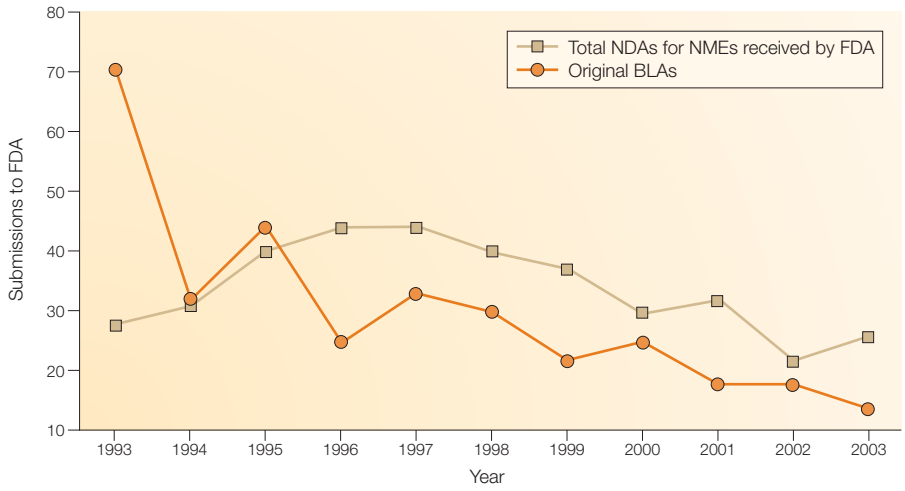

Figure 1 | **Ten-year trends in major drug and biological product submissions to the FDA.** Based on data from REF. 6.

The existing model of drug development in the pharmaceutical industry faces daunting challenges. More than 80% of potential products that enter the development pipeline with the filing of an IND fail to make it to market because of fatal flaws in one or more of the three dimensions of product development: first, drug safety (a high incidence of adverse events or unexpected toxicity); second, drug efficacy (no strong signal of effectiveness over placebo and/or active comparator); and third, industrialization (the product cannot be manufactured at a commercial scale with consistently high quality). Furthermore, it has been estimated that to develop a single, successful new chemical entity now costs in excess of US $800 million[1] (a figure that includes 'opportunity costs'), and the average time taken to do so is 8–10 years. The clinical component of the overall cost of new drug development is ~58% or US $400 million[1]. A significant proportion of these dollars goes towards supporting the Phase III randomized controlled trials (RCT) that provide the most convincing evidence of the safety and efficacy of a drug product. However, from a recent report, one can estimate the failure rate in Phase III trials to be ~50%[2].

Variability in drug response

Variability in drug response is a major barrier to successful drug development. As Sir William Osler said in 1892 about the practice of medicine, "If it were not for the great variability among individuals, medicine might as well be a science and not an art". PGx and PGt provide the scientific tools that enable us to explore the pathophysiological mechanisms underlying these differences in drug response at the molecular level. We expect that there will be an increase in the public demand for more science and less art in the search for better and more effective therapies to reduce the morbidity and mortality of chronic diseases such as hypertension and cancer. In order to improve the 'art' and the productivity of the drug development process, PGx and PGt can improve the predictability of preclinical safety studies, and clinical safety and efficacy trials.

A key to increasing R&D success is identifying drugs that are likely to either succeed or fail late in the process early in the drug development process and thereby reduce attrition in Phase III trials — that is, before the high costs of these trials are incurred by a sponsor. This is an important achievement because the average size of a Phase III clinical trial has nearly tripled in the past 20 years. It does not make much sense to wait until a Phase III trial fails to try to establish why the drug did not provide evidence of efficacy or lack of toxicity, and how to design the next trial; that approach is expensive and time consuming.

It is typical that each Phase III trial is preceded by a much longer preclinical and early clinical work-up of the drug, so what is needed is an increased ability to predict Phase III success or failure, aimed at the preclinical and early clinical time period. For example, in terms of cost, a 10% improvement in predicting failure before large-scale Phase III clinical trials begin could save ~US $100 million in development costs. Other opportunities for saving US $12–21 million dollars in direct development costs can be attained by shifting just 5% of clinical failures from Phase III to Phase I, or by shifting 25% of failures from Phase II to Phase I[3].

The major causes of attrition of drugs in late-phase clinical trials are lack of efficacy or concerns about safety. To achieve increases in productivity and success, effective scientific development tools, such as those provided by PGx and PGt, are needed to predict product performance — whether it be success or failure — with a high degree of certainty, and this needs to occur both early and reliably in the development process. For example, PGx biomarkers can be used to identify potential responders. By stratifying patients by biomarker status in Phase II clinical trials, populations with a high probability of responding can be identified, thereby simplifying Phase III trials and increasing their probability of success.

Clearly, modern innovative tools are needed to predict the performance and manufacturing quality of twenty-first century products. Although it seems that everyone agrees with this premise, the problem is that the drug development process is no longer able to keep pace with the rate and scope of discoveries in basic science. For example, although imaging-based biomarkers are presently being used to develop drugs for Alzheimer's disease, there has not been a successful strategy for correlating anatomical imaging with primary clinical endpoints of cognition and function to enable the identification of new drug candidates that can modify disease progression. The tools currently used in drug discovery and development — the so-called 'critical path' tools — have not incorporated either the latest advances in biomarker technologies (with links to clinical outcomes), the basic and information sciences (such as the new knowledge and technologies provided by the rapid development of genomic research), or innovations in clinical sciences (for example, adaptive trial designs) to substantially affect the success of drug development and improve the quality of public health. Although the reasons underlying the failures of drugs in development (especially those failing in late-phase clinical trials), and inefficiencies in the development process in general, are not well understood, many suspect that a lack of understanding of variability in drug response between patients is a key part of the problem. Recent and rapidly accumulating evidence is beginning to point toward genetic and genomic factors, alone and taken together with environmental factors, as being of considerable importance in determining inter-individual variability in drug responses.

An example of the power of PGx is evident from recent publications regarding gefitinib (Iressa; AstraZeneca)[4,5]. Gefitinib is one member of a new class of targeted cancer therapies that inhibit the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), which is important in many cancers. Gefitinib

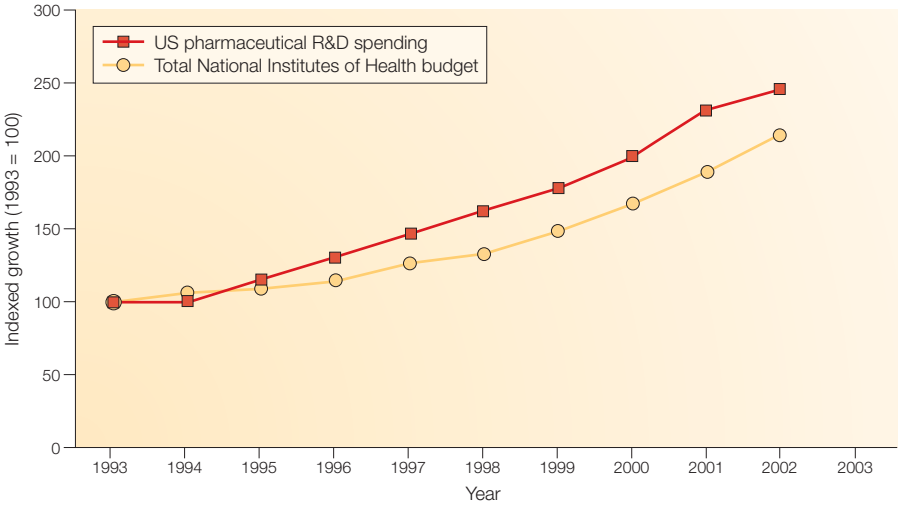

Figure 2 | **Ten-year trends in biomedical research spending.** Source: Parexel's Pharmaceutical R&D Statistical sourcebook 2002/2003.

was approved by the FDA for advanced non-small-cell lung cancer (NSCLC) in May 2003. The overall response rate at approval, as measured by significant tumour shrinkage, was less than optimal and occurred in only about 10% of patients who were administered gefitinib. However, clinician reports indicated that the drug works rapidly and amazingly well in some patients. In addition, higher response rates were noted in Japanese subjects, women and patients with adenocarcinoma.

PGx provides a molecular explanation for why gefitinib is so much more effective in some patients, whereas others seem insensitive to it. For example, Lynch *et al.* identified somatic mutations in the tyrosine kinase domain of the *EGFR* gene in eight out of nine patients with lung cancer characterized as 'responders', and in none of seven patients who had no response. A genomic approach to identifying responder subsets would clearly be advantageous given the potential safety consequences (for example, interstitial lung disease) in patients who have a small chance of benefiting from gefitinib treatment. Screening for these mutations in lung-cancer patients earlier could possibly identify responders and facilitate earlier treatment and thereby reduce disease progression.

If such findings are generalizable, they could markedly improve development of further EGFR tyrosine kinase inhibitors. For example, future clinical trials for such drugs intended to treat NSCLC might include screening for EGFR mutations in Phase II (hypothesis-generating) trials to identify patients who would then have a greater likelihood of a beneficial response. This drug development strategy would lead to Phase III trials enriched with patients with EGFR mutations that would have a higher probability of successfully demonstrating efficacy. This approach could reduce the risk of treatment failure, and could decrease the size and cost of subsequent Phase III trials, thereby bringing greater efficiency to the development process. At a minimum, this type of genomic information could also help understand the drug better by identifying the root cause of variability in responsiveness. This is not to suggest that a new drug should not be tested in patients who test negative for the mutation of interest, unless it is obvious that the drug could not work in this group. If a pharmacogenomic test is not intended to be available in clinical practice to direct drug treatment to the patients demonstrated to be responders based on a mutation, then data in the subgroup that tests negative will be needed to assess the benefit/risk ratio in the overall population during the drug development process.

The Critical Path

The FDA released a white paper on 16 March 2004 entitled *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products*[6]. This white paper is a serious attempt by the FDA to bring attention and focus to the need for targeted scientific efforts to modernize the tools, techniques and methods used to evaluate the safety, efficacy and quality of drug products. It describes the urgent need to build bridges among constituencies such as the FDA, the National Institutes of Health and the private sector to modernize the development process for medical products — the Critical Path — to make product development more predictable and less costly.

The critical path is defined as the path from candidate selection to product launch and it defines the potential bottlenecks in bringing a product to market. The focus of the critical path initiative is to identify ways to update the product development infrastructure for drugs, biologics and devices, and the evaluative tools currently used to assess the safety and efficacy of new medical products. Examples of evaluative tools include: better pathophysiological cell and/or animal disease state models for preclinical screening of new molecules; new and innovative scientific approaches, such as the use of BAYESIAN STATISTICS; the use and verification of pathophysiological and/or descriptive biomarkers for patient selection for clinical trials and/or use as surrogate endpoints; the use of modelling and computer simulation to design clinical trials and/or predict failures of medical devices; and improvement in processes for post-market reporting of adverse events related to implanted devices. In addition, an important example of a scientific opportunity for improving the critical path is the use of PGx and PGt, or, more specifically, the identification of DNA-based biomarkers or RNA-expression profiles that can provide insights into the stage of a disease, disease progression, drug response and drug-dosing requirements, and thereby lead to the development of tests to predict clinical outcomes more reliably.

The FDA's aim to advance PGx

The FDA's mission includes protecting and advancing public health, and encouraging innovations that make medicines and foods more effective, safer and more affordable. Beginning in earnest in June 2001, the FDA took the lead with several key initiatives in PGx and PGt that are intended to stimulate the use of PGx and PGt technologies in drug development, and to foster improvements in drug product safety and efficacy. After publication of a forward-looking paper that provides a regulatory perspective on the opportunities and challenges of integrating pharmacogenomics into drug development and regulatory decision-making[7], the FDA has coordinated its efforts with the pharmaceutical and biotechnology industries to convene a series of public PGx and PGt workshops. These workshops are a structured effort to bring together stakeholders from industry and academia with FDA scientists to openly discuss the status of PGx and PGt technology, the use of PGx and PGt in drug development and therapeutics, and the specific strategies that are most needed for using PGx and PGt as a tool to facilitate more efficient and effective research along the critical path of drug development.

Publications of the proceedings of these workshops are valuable references that describe the current status of PGx and PGt in drug development, and what is needed to continue to advance this critical path tool[8–10].

New drug development. The culmination of many individual efforts within the FDA, and the public input derived from the synergistic FDA–industry co-sponsored workshops, led to a significant milestone in the advancement of PGx: the November 2003 publication of the *Draft Guidance for Industry: Pharmacogenomic Data Submission* (see link to document in further information). This guidance was timely, in that there was considerable uncertainty and fear about what the FDA would do with exploratory genomic data obtained during the new drug development process, a fear that was a stumbling block for many pharmaceutical companies. The major concern was that the FDA would overreact to non-validated, exploratory genomic biomarkers, take them out of context, misinterpret them, cause delays in drug development, request additional clinical trials and/or put clinical trials on hold. This concern led to a reluctance of the industry to introduce genomic studies into their drug development plans.

The FDA wanted to break down these real or perceived barriers and motivate drug developers to consider PGx and PGt strategies seriously in their drug development portfolios. The PGx data guidance proposed a new pathway for industry and others for submitting non-clinical and exploratory clinical genomic data during the IND period without it undergoing formal regulatory review, and describes the submission format and regulatory review of such data by the Interdisciplinary PGx Review Group (IPRG). It introduced some new concepts related to genomic biomarkers and defined categories of biomarkers; that is, exploratory biomarkers, valid biomarkers, probable valid biomarkers and known valid biomarkers. By design, the guidance shied away from presenting very specific recommendations for biomarker validation and formats for submitting genomic data to avoid hindering progress in the field — the FDA recognized that the science is still evolving.

Important components of the guidance are three decision algorithms or decision trees based on the categories of biomarkers and the stage of drug development. Generally, most genomic data submitted to the FDA to date has been exploratory and not suitable for regulatory decision making. Such data — for example, those derived from gene-expression microarrays — have either no clear pathophysiological correlates, and/or are not crucial for entering patients into clinical trials or supporting claims about safety, efficacy and/or dosing. Valid biomarkers are defined as those biomarkers measured in an analytical test system with well-established performance characteristics and with an established scientific framework or body of evidence that explains the physiological, pharmacological, toxicological or clinical significance of the test results. Known valid biomarkers are those broadly accepted in the scientific community, whereas probable valid biomarkers are those that seem to have predictive value for clinical outcomes, but which have not yet been widely accepted or independently replicated. The decision trees can be used to determine when genomic data can be submitted voluntarily, and when submissions of the data are required by FDA regulations. In addition, the guidance describes the format (for example, full report, abbreviated report, synopsis or voluntary submission report) for submitting such data.

An example of one of the decision trees from the guidance that illustrates the process for submitting PGx data to an IND, as either a required submission or as a voluntary genomic data submission (VGDS), is shown in FIG. 3. It should be noted that the process by which industry submits VGDSs to the FDA uses the existing path for IND (or as a pre-IND in some cases) or NDA submissions, which assures the sponsor of the confidentiality of their data.

The FDA hopes that voluntary submissions will benefit both the industry and the Agency, and will provide a rational scientific basis for future data standards and genomic policies. Information and knowledge gained from voluntary submissions will be shared publicly across submissions in a way that protects the proprietary interests of companies. The FDA is currently in the process of finalizing the *Draft Guidance* on pharmacogenomic data submissions, and is writing two other internal documents that will describe the process for sponsors submitting VGDS and the roles and responsibilities of the IPRG.

Improving approved drugs. The FDA has a long-standing interest in 'individualization factors', such as those defined by intrinsic factors (for example, age, gender, race, renal dysfunction and genetics) and extrinsic factors (for example, food, co-administered drugs, smoking and alcohol). The Agency believes that an appreciation of controllable sources of variability in drug action and potential injury to patients should be achieved before the marketing of new pharmaceutical products[11]. Information on these important co-variates influencing drug safety and efficacy are generally reported in various sections of the product package insert. PGt, or more specifically the patient genotype, has been shown to be a clinically relevant co-variate for drugs approved recently, as well as those approved decades ago. Understanding the PGt of a drug is the first step towards developing a predictive test to optimize therapeutics.

A recent example of the role that PGt played in the labelling of a new drug is the case of atomoxetine (Strattera; Eli Lilly). This drug was approved by the FDA in November 2002 for attention-deficit/hyperactivity disorder with a fixed dose of 0.5 mg per kg to be titrated up to 1.2 mg per kg. The drug is metabolized by cytochrome P450 2D6 (CYP2D6) with a clearance of 0.35 l per h per kg in extensive metabolizers (EM) and 0.03 l per h per kg in poor metabolizers (PM). The ratio (PM/EM) of the AREA-UNDER-CURVE (AUC) for plasma atomoxetine was ~10. The sponsor did a sensible analysis of adverse events in clinical trials by looking at a post-facto stratification of patient subsets defined by genotype. The frequency of adverse drug reactions (ADRs) — primarily insomnia and irritability — was 9% in PMs and 6% in EMs. There were no major differences in serious ADRs between PMs and EMs.

The label of atomoxetine mentions CYP2D6 in seven different sections, including those describing pharmacokinetics, drug–drug interactions, adverse events and laboratory tests. However, the evidence did not warrant recommending that a pharmacogenetic test for *CYP2D6* status be done before prescribing the drug, but it did provide descriptive information that could be used along with other observations (for example, an adverse event) to guide clinician decisions about an individual's need for dosing adjustment. This example demonstrates the value that pharmacogenetic information in a package insert can bring to the use of a drug, including knowledge related to genotype (for example, *CYP2D6*3*), phenotype (for example, poor metabolizers) and clinical outcomes (for example, adverse events) that can increase the quality of a clinician's decision about individualizing drug treatment.

The atomoxetine example also brings to mind several challenges that face sponsors, regulatory agencies and clinicians in translating genotype information from research to the clinic. First, what is the best way to define PMs in a research setting? The PM phenotype can be determined by the urinary metabolic ratio, the observed AUC or plasma clearance of the drug in different genotype subsets. There are more than 40 ALLELES of *CYP2D6*, and about 25% of these have greatly decreased

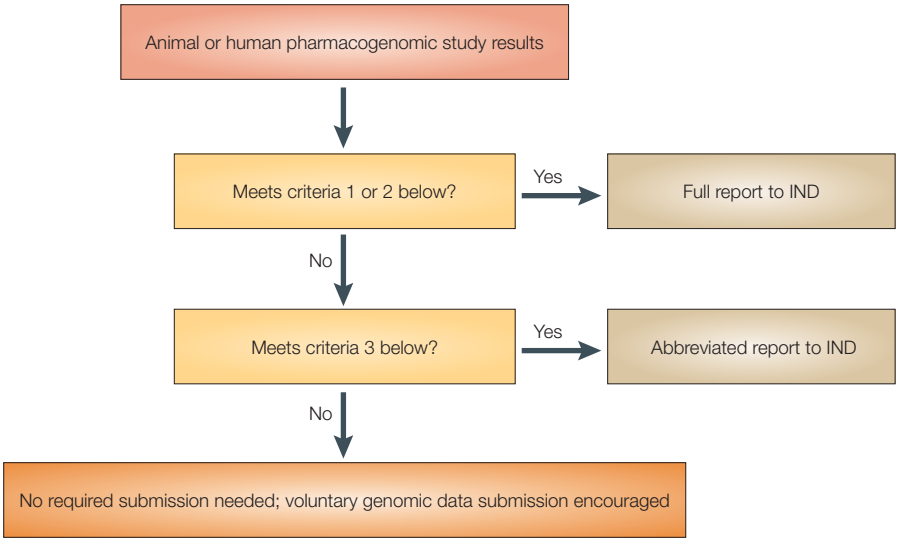

Figure 3 | **An example of a decision tree for submitting pharmacogenomic data during the IND period as a required submission or as a voluntary genomic data submission.** Pharmacogenomic data must be submitted in the Investigational New Drug application (IND) under CFR 312.23 if *any* of the following criteria apply: first, the test results are used for making decisions pertaining to a specific clinical trial, or in an animal trial used to support safety (for example, the results will affect dose selection, entry criteria into a clinical trial, safety monitoring or subject stratification); second, the test results are being used to support scientific arguments pertaining to, for example, the pharmacological mechanism of action, the selection of drug dosing or the safety and effectiveness of the drug; and third, the test results constitute a known valid biomarker for physiological, pathophysiological, toxicological or clinical states and/or outcomes in humans, or is a known valid biomarker for a safety outcome in an animal study. If the information on the biomarker (for example, human *CYP2D6* status) is *not* being used for the purposes described in the first two points above, the information must be submitted to the IND as an abbreviated report. Adapted from Appendix A in the *Guidance for Industry: Pharmacogenomic Data Submissions*.

or null activity. There is also significant variability in the frequency of null alleles of *CYP2D6* in different racial or ethnic groups. So, an open question remains: what alleles should be studied in drug development, and how should this information be translated into a product's package insert?

Second, how should PGt information be reported in the label? This raises two sub-issues: whether or not to report only phenotype data (for example, PMs and EMs), or specific alleles of CYP2D6 (for example, *3, *4 and *5); and the question of who will interpret the significance of these data with respect to dosing, safety and efficacy.

Third, if PGt information is included in the label of a drug product in a way that gives physicians and patients an option to have a genomic test done as part of therapy, this raises translational issues that include public knowledge that the test is available, the quality of the test results, its cost and the proper interpretation of test results.

Despite the high expectations that have surrounded the Human Genome Project, and the frequent reports of the discovery of genes that control a variety of diseases and variability in drug response, there has been relatively little translation of this information into drug development and even less into clinical practice. The FDA believes that there is value in applying long-established PGt to older, marketed drugs in the post-marketing period to improve their risk/benefit ratio by optimizing or individualizing dosing. Examples of older drugs that could benefit from PGt are 6-mercaptopurine (6-MP); azathioprine and 6-thioguanine (6-TG), each of which are substrates for thiopurine methyltransferase (TPMT); irinotecan (a substrate for uridine diphosphate glucoronosyltransferase (UGT1A1)); and warfarin (a substrate for CYP2C9). Each of these drugs has a narrow therapeutic range, wide inter-individual variability in dosing requirements, and frequent and serious safety problems. The genes encoding each of the enzymes mentioned above can exist in one of several isoforms (for example, *TPMT*2*, *UGT1A1*28* and *CYP2C9*3*) and these enzymes are mostly found in either red blood cells (in the case of TPMT) or the liver (for UGT1A1 and CYP2C9). Certain mutations in these isoforms, or gene variants, produce different phenotypes, but the most important factor for drug dosing is the PM phenotype that results in heightened exposure to either the parent drug or a major metabolite, or reduced exposure to an active metabolite (for example, morphine from codeine administration).

In July 2003, the FDA Pediatric Subcommittee of the Oncology Drug Advisory Committee (ODAC) discussed whether or not the package insert of 6-MP should be updated to include information on *TPMT* genotypes. 6-MP was approved decades ago for use in children with acute lymphoblastic leukaemia (ALL) and, taken orally together with methotrexate and/or other chemotherapeutic agents, is the backbone of continuation therapy. The dose intensity of 6-MP is a major determinant of both event-free survival (efficacy) and NEUTROPENIA (safety). The clearance of 6-MP, and therefore exposure to active moieties, is dependent on its conversion to 6-MMP (inactivation via the TPMT pathway) and 6-TG (active nucleotides). More than 11% of individuals in Caucasian populations are heterozygous or homozygous carriers of TPMT null alleles (intermediate or poor metabolizers), which results in the excess accumulation of 6-TG at the expense of 6-MMP formation. There are three major genotypes in the population, each with a range of TPMT activity (high, intermediate and low), and each with a different relative risk of developing neutropenia when administered the standard dose of 6-MP (50 mg per m^2). The PM genotype, which has an incidence of 1 in 300, accumulates excess 6-TG that is nearly certain to lead to severe and potentially fatal bone-marrow toxicity. It has been recommended that the usual dose of 6-MP be reduced by 80–90% for the PM genotype to reduce the risk of neutropenia.

On the basis of the evidence presented in July 2003, the Subcommittee considered the consequences of a label revision thoroughly, and in the end recommended that the label of 6-MP should be updated with current information on *TPMT* genotypes, but stopped short of recommending that testing for *TPMT* status be mandatory before prescribing 6-MP. The experts on the subcommittee considered many factors in making their recommendation, some of which follow: first, the scarcity of prospective clinical trials to support specific recommendations about dose reduction in patients who were either heterozygous or homozygous for null alleles; second, the wide inter-individual variability in TPMT activity, in particular for patients with one variant TPMT allele, and the subsequent risk of reducing effectiveness if doses are reduced erroneously; third, the potential benefit and cost of TPMT genotyping as compared with current phenotyping based on TPMT activity in red blood cells

Glossary

ALLELES
Different or alternative forms of the same gene that can occupy a particular locus on a specific chromosome. Humans have two alleles at that location, one on each chromosome of a homologous pair.

AREA-UNDER-CURVE
(AUC). A metric that summarizes serum or plasma drug concentrations measured over time (for example, 24 hours) in a given individual following the administration of a drug. The AUC is interpreted as the total systemic exposure and is an index of how much of a drug reaches the bloodstream in a set period of time. AUC is also a means to compare the bioavailability of drug from a drug product.

BAYESIAN STATISTICS
A statistical method of analysis that incorporates prior knowledge (for example, on safety and efficacy parameters), specifications of prior distributions and accumulated clinical data experience into making probability calculations and designing future clinical trials.

BIOLOGIC LICENSE APPLICATION
A formal application analogous to a New Drug Application, but for biotechnology-derived pharmaceuticals (for example, complex, large molecules).

BIOMARKER
A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention.

HAPLOTYPE
A set or combination of alleles or linked genetic markers found on a single chromosome, which tend to be inherited together in a given individual.

INVESTIGATIONAL NEW DRUG APPLICATION
Before initiating any clinical trials of a new drug in humans, a drug sponsor must submit an Investigational New Drug application (IND) to the FDA. The IND contains three broad categories of information: data from animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information.

NEW DRUG APPLICATION
A formal application that serves as a vehicle through which sponsors propose that the FDA approve a new pharmaceutical (for example, traditional small molecules) for sale and marketing in the United States. When the investigational phase of a drug is completed, the manufacturer submits the results of all the studies to the FDA in a New Drug Application (NDA) for review by FDA officials. The purpose of the NDA is for the FDA to decide if the drug meets the statutory standards for safety, effectiveness and benefit/risk for its intended use, and labelling and manufacturing quality.

NEUTROPENIA
An abnormal decrease in the number of white blood cells in the blood (as measured by an absolute neutrophil count), which increases the risk of infection and fever. It usually occurs as a result of chemotherapy.

SINGLE-NUCLEOTIDE POLYMORPHISM MAPS
A diagram or overview of a stretch of DNA containing single-nucleotide polymorphisms (SNPs). SNPs are DNA sequence variations that occur when a single nucleotide (A, T, C or G) in the genome sequence is altered in different individuals. A map of SNPs across the genome allows genetic traits to be localized by statistical association with the specific region of the genome that is marked by the SNP or multiple nearby SNPs.

coupled with observations of early neutropenia; and fourth, the widespread availability of TPMT testing.

This illustrative example demonstrates that PGt can, in fact, make a contribution to drug safety by guiding doctors towards appropriate dosing. However, translating PGt information from research to the clinic for older drugs is in some ways more challenging than for newer drugs, for the reasons cited above. The three categories of issues or questions raised as challenges following the atomoxetine example also apply to older drugs. However, there are, in addition, other issues and questions that need to be resolved.

First, what is the best way to educate clinicians about the advantages and limitations of adopting a PGt test for a drug that they have been using, albeit not optimally, for decades? This is particularly pertinent for cases such as 6-MP, for which the assessment of neutropenia or another test (for example, TPMT activity in red blood cells) has been used phenotypically as a rough guide to reduce the intensity of dosing.

Second, how should the dosing of a drug such as 6-MP be adjusted, based on genotype, when there is an absence of prospective clinical trials to demonstrate the efficacy of the reduced dose? This is a relevant question in the case of 6-MP, for which the success rate of event-free survival in childhood ALL is nearly 80–85% and evidence supporting the reduction of dose in patients with intermediate TPMT activity is not substantial. Patients with high TPMT activity relative to a given dose might not receive the maximum benefit from the drug because of rapid clearance.

Third, when is the best time for genotyping of patients being administered 6-MP for their TPMT activity status? Options include routinely genotyping TPMT before initiation of 6-MP, genotyping TPMT within the first week of receiving 6-MP or genotyping TPMT only in the case of overt neutropenia.

However, as the Pediatric Subcommittee of ODAC pointed out, genotyping TPMT activity is not a substitute for careful monitoring of white-blood-cell counts in patients receiving 6-MP, but an adjunct. TPMT testing, when combined with other tests and observations, can lead to higher-quality decisions about drug selection and drug dosing that will further decrease the risk of severe and preventable bone-marrow suppression. The FDA is in the process of revising the 6-MP label on the basis of the recommendations of the Subcommittee and is deliberating all of these challenges in translating PGt data into useful information for practitioners and their patients.

Conclusion

The FDA has become a proactive and thoughtful advocate of PGx and PGt, and believes that as a public health Agency it has a responsibility to play a leading role in bringing about the translation of PGx and PGt from bench to bedside. The FDA also realizes that it can hinder innovation and become a regulatory barrier in the translational process if it is not careful with its guidance, policies and procedures. The Agency hopes that pharmaceutical companies view advances in PGx and PGt as an opportunity and one kind of investment in R&D that can help bring a fresh approach to addressing the 'pipeline' problem outlined in the FDA Critical Path white paper.

We believe that PGx and PGt have the potential to revolutionize the drug development process, making it more efficient and bringing value to patient care, including more diagnostic or test products to individualize therapy. This could, in retrospect, seem to have taken much longer than was anticipated but we feel that progress is being made. Regulatory agencies, pharmaceutical companies, the clinical community, third-party payers and patient-advocacy groups are all interested in strategies that can improve the cost, quality and time of drug development, and reduce the risks associated with drug therapy in patients. We do not expect that big changes in these areas will happen overnight with one seminal event or be straightforward to implement, but rather will occur in a more evolutionary or iterative manner, such that progress builds on one successful application of PGx or PGt after another — which now seem to be occurring more rapidly.

We acknowledge that there are, and will continue to be, many different kinds of challenges in translating PGx and PGt from bench to bedside, ranging from issues of historical practices, cost, test availability and reimbursement, to issues of science, biomarker validation, education and adoption of PGx and PGt tests into clinical practice. But, as has been highlighted by the promising results with gefitinib, and the tried and true examples of atomoxetine and 6-MP, these challenges are being met and overcome to benefit both the science of drug development and the quality

of public health. The FDA can be influential and will play an important role in collaborating with others in translating the important discoveries of PGx and PGt from bench to bedside.

But we also need to be on guard. We are aware that drug development is a global enterprise, and therefore international collaboration between regulatory agencies must continue to grow further to harmonize guidance and policies in a way that facilitates and not complicates the drug development process. We must also strive harder to engage the various stakeholders and constituencies, in both the private and public sectors, in conversation regarding effective strategies to advance PGx and PGt. It is clearly in the interest of everyone to streamline the pre-approval drug development process (in terms of cost, time, early attrition, and late-phase success) and reduce the likelihood of toxicity in the post-approval period. We hope that others view the key initiatives and strategies adopted by the FDA — the Critical Path white paper, and its advocacy of PGx and PGt — as a willingness to work together to link bench discoveries to bedside benefits, and we look forward to continued involvement.

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1. DiMasi, J., Hansen, R. W. & Grabowski, H. G. The price of innovation: new estimates of drug development costs. *J. Health Econ.* **22**, 151–185 (2003).
2. Gilbert, J. Rebuilding big PhRMA's business model. *In Vivo* November, 73–80 (2003).
3. Tufts CDSS quantifies savings from boosting new drug R&D efficiency. *Tufts CSDD Impact Report* **4**, 1–4 (2002).
4. Lynch, T. J. *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *N. Eng. J. Med.* **350**, 2129–2139 (2004).
5. Guillermo Paez, J. *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib. *Science* **304**, 1497–1500 (2004).
6. *Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products* [online], <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html> (2004).
7. Lesko, L. J. & Woodcock, J. Pharmacogenomic-guided drug development: regulatory perspective. *Pharmacogenomics J.* **2**, 20–24 (2002).
8. Lesko, L. J. *et al*. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PHRMA-DRUSAFE workshop. *J. Clin. Pharmacol.* **43**, 342–358 (2003).
9. Salerno, R. A. & Lesko, L. J. Pharmacogenomics in drug development and regulatory decision-making: the genomic data submission (GDS) proposal. *Pharmacogenomics* **5**, 25–30 (2004).
10. Salerno, R. A. & Lesko, L. J. Pharmacogenomic data: FDA voluntary and required submission guidance. *Pharmacogenomics* **5**, 503–505 (2004).
11. Peck, C. C., Temple, R. T. & Collins, J. Understanding consequences of concurrent therapies. *JAMA* **269**, 1513–1518 (1993).

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Competing financial interest
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