DNA, drugs and chariots: on a decade of pharmacogenomics at the US FDA

Over the past 10 years, the US FDA has become a strong pharmacogenomics advocate as part of its mission to both protect and advance public health by enabling innovations that make medicines safer to use and more effective. The agency has evolved its advocacy cautiously on a foundation of science-based information from novel programs, such as the Voluntary Genomics Data Submission initiative, and on careful regulatory assessment of the extraordinary advances in clinical pharmacogenomics that have supported the update of drug labels with genetic information. This commentary goes into detail on the evolution of these achievements. However, many challenges remain for pharmacogenomics, and they will continue to evolve, and all stakeholders must work together. As the decade draws to a close, we have presented four major areas that need to be addressed collectively to assure that pharmacogenomics continues to mature over the next 10 years into a science that is essential to the practice of medicine.

KEYWORDS: FDA • genomics • personalized medicine • pharmacogenomics • regulatory

“By 2015, we will see the beginnings of a real transformation in the therapeutics of medicine, which by 2020, will have touched virtually every disorder … and the drugs that we give in 2020 will, for the most part, be those that were based on the understanding of the genome, and the things that we use today will be relegated to the dust bin.”

Francis Collins, Former NHGRI Director, 13th February (2005)

Dr Collins’s mid-decade vision was not unrealistic at the time, given the exponential growth in genomic information that came in the 5 years after the draft of the human genome, which was published in 2000. However, our ability to apply knowledge of human genome variability to the discovery, development and clinical translation of personalized medicines is still rather elementary. At the beginning of the decade, pharmacogenomics (PGx) was generally perceived to be a rapidly evolving science with the potential to improve risk–benefit for given patients treated with already available drugs. In addition, a real promise of PGx was to bring innovation to the pharmaceutical and biotechnology drug-development process. There was significant concern regarding the growing costs, and increasing time lag, of developing a new molecular entity from the discovery stage to market approval. Innovation was deemed essential to reduce the attrition rate in late-phase clinical trials and to improve the overall productivity of the drug-development enterprise. Regulators at the US FDA recognized this potential too. However, FDA reviewers had relatively little experience with actually providing regulatory advice regarding PGx in investigational new drug applications, or assessing PGx data in new drug applications and biological licensing applications.

Despite a lack of formal infrastructure for dealing with genetics and genomics in therapeutic marketing applications, the idea that certain subpopulations (defined genetically or otherwise) are more likely to respond to certain treatments was well appreciated in the agency. For example, the FDA approved the original application for trastuzumab (Herceptin®) in September 1998 with indications for single-agent use as second- or third-line therapy for metastatic breast cancer, and in combination with paclitaxel as first-line treatment. The label recommended that trastuzumab should only be used in patients whose tumors have HER2 protein overexpression (~25% of all breast cancers) because the beneficial treatment effects were largely limited to these patients. The Herceptin
example represented a prototype, with unique strengths and weaknesses, for the subsequent development and regulatory review of targeted therapies in the subsequent decade.

Early FDA initiatives
In the early 2000s, it was clear to the FDA that the pharmaceutical and biotechnology industries had been conducting exploratory genomic investigations for over 10 years, but the industries were reluctant to share these data with the FDA. Their concerns were that reviewers would prematurely use exploratory data to make inappropriate regulatory decisions or request additional studies from the companies. To encourage the further integration of genomics in drug development, Lesko and Woodcock published two papers that provided a regulatory perspective on PGx, laid out the challenges ahead and highlighted recent FDA initiatives to advance PGx and promote its uptake into clinical practice [1,2]. There was a major effort to foster the exchange of PGx information between the FDA and the industry, so a series of Drug Information Association (DIA) co-sponsored workshops began in May 2002 with important goals, which was to identify barriers to PGx, and to gain public input on what is needed in terms of FDA Guidances for Industry [3]. A key achievement of the 2002 workshop was the introduction of a ‘safe harbor’ concept for submission of exploratory PGx data to the FDA. A draft of the guidelines on voluntary genomic data submissions (VGDS) were published by the FDA in November 2003; this proposed process was discussed extensively at the second DIA co-sponsored workshop in November 2003 and the final guidelines were issued in March 2005 [101].

By all indications, the industry reaction and the impact of the guidelines has been a reasonable success. As of December 2009, the FDA has received over 40 voluntary genomic data submissions. There has also been a dramatic increase in regular investigational new drug applications, new drug applications and biological licensing applications submissions that contain genomic information. Just between 2008 and 2009, there has been more than a 250% increase in review workload by the genomics group in the Office of Clinical Pharmacology at the FDA.

FDA update of labels
At the beginning of the decade, the FDA began looking for opportunities to improve the quality of therapeutics using already marketed drugs by updating the labels to include PGx information. The Pediatric Oncology Subcommittee of the Oncology Drug Advisory Committee met in July 2003 to review data related to the use of 6-mercaptopurine (6-MP) in childhood acute lymphoblastic leukemia and the impact of thiopurine S-methyltransferase genotype on 6-MP-induced myelosuppression. The Committee agreed that the label of 6-MP (Purinethol®) should be updated and TPMT information was added to the Clinical Pharmacology, Warnings, Precautions, Adverse Reactions, and Dosage and Administration sections of the 6-MP label. Subsequently, other milestone PGx-related label updates were achieved for irinotecan (Camptosar®), linking UGT1A1 mutations with increased susceptibility to neutropenia (2005), warfarin (Coumadin®), linking CYP2C9–VKORC1 combination genotypes with variable dose requirements (2007 and 2010), carbamazepine (Tegretol®), linking variants in the gene HLA-B*1502 with increased risk of developing life-threatening skin reactions (2007), abacavir (Ziagen®), linking HLA-B*5701 with higher risk of a hypersensitivity reaction (2008), panitumumab (Vectibix®) and cetuximab (Erbitux®), linking KRAS mutations with a lack of a treatment benefit in patients with metastatic colorectal cancer (2009) and clopidogrel (Plavix®), linking CYP2C19 poor metabolizer status with a diminished antiplatelet response and higher cardiovascular event rates than CYP2C19 extensive metabolizers (2009 and 2010). A representative listing of both new and previously approved drugs whose labels contain genomic information can be found in the online FDA Table of Genomic Biomarkers [102].

Lessons learned
Industry sponsors have not fully embraced the VGDS concept as evidenced by the fact that numerous major pharmaceutical and biotechnology companies have never submitted a VGDS to the FDA. Their reasons are unclear, but may be owing to residual apprehension about the FDA review of voluntary genomic data, confusion over the requirements of a voluntary submission versus a required submission or the perception that it is not worth the time or effort to prepare and submit a VGDS. The potential for PGx in drug development envisioned 10 years ago has been mostly unfulfilled; this does not necessarily mean that the concept of ‘personalized medicine’ is invalid, but rather it reflects the overhyped view that PGx would transform drug development and therapeutics more rapidly. Given that it takes a company up to 8–12 years to complete the clinical development a molecule needs for regulatory
approval, a decade of time is a relatively short timeframe. Nevertheless, while most of the progress in genomics during the past 10 years has been in the field of oncology (e.g., imatinib/C-KIT expression, erlotinib/EGF receptor [EGFR] expression and dasatinib/Ph+), there have been advances in the area of HIV and AIDS (e.g., maraviroc/CCR5 tropism), the use of PGx for guiding dosing (e.g., tetrabenazine/CYP2D6), and the use of PGx to differentiate a molecule from a competing molecule in the marketplace (e.g., prasugrel/CYP2C19).

Each label update has provided a unique opportunity to better understand the nuances of adding PGx to labels and the subsequent impact of label updates on adoption into clinical practice and diagnostic test reimbursement. The following represents some ‘first in label updates’ from the past 10 years along with some personal perspectives.

6-MP/TPMT
This was the first label to be updated in the last decade. There was a strong, mechanistically supported association between low TPMT enzyme activity (one in 300) and intermediate TPMT enzyme activity (11 in 100), increased concentrations of thioguanine derivatives at standard doses, and increased risk of myelosuppression. No specific doses of 6-MP were recommended in the label, although high-volume cancer centers (and later gastrointestinal practices) were developing dose-reduction schemas based on PGx and pharmacokinetic principles. TPMT testing does not obviate the need for monitoring complete blood count and platelet counts and looking for symptoms of myelosuppression. Clinical adoption of TPMT testing appears to be relatively low in cancer patients prescribed 6-MP (e.g., as compared with HER2 testing for trastuzumab) but there has been a more widespread uptake of TPMT testing in patients needing immunosuppressive therapy, including those receiving other thiopurines (e.g., azathioprine).

Irinotecan/UGT1A1*28
This was the first label update to recommend a specific dosing reduction based on PGx (at least one level dose reduction as defined in the package insert) in patients homozygous for UGT1A1*28 because of an increased risk of neutropenia. There is a fairly well-understood causal link between dose, exposure levels of irinotecan’s active metabolite, and its association with risk of neutropenia. There were no specific recommendations for prescreening patients before receiving irinotecan and clinical adoption appears to be progressing slowly.

Warfarin/CYP2C9–VKORC1
The first label update in 2007, which was based on a combination genotype, related to both the pharmacokinetics (CYP2C9 gene variants) and pharmacodynamics (VKORC1 gene variants) of the drug. It received a high amount of attention because of the widespread use of warfarin and the well-known risks of minor and major bleeding. The label did not dictate how physicians should change the dosage based on genotype. Clinical adoption appears to be relatively low at present; however, the 2007 warfarin label update was followed by a significant amount of new research to improve understanding of the role of genotype-guided dosing. This led to a 2010 update of the label in which specific ranges of initial doses were assigned to each genotype representing the expected steady-state maintenance doses.

Carbamazepine/HLA-B*1502
This was the first label update to include a strong association between a serious adverse event, Stevens–Johnson syndrome, and inherited variant in the gene based on relatively few cases (<125). The mechanism is unclear but consistent with other gene–drug pairs in which hypersensitivity is of concern. The gene variant is found almost exclusively in patients with Southeast Asian ancestry, potentially allowing for targeted genotyping. There is a boxed warning to prescreen patients with ancestry in genetically at-risk populations. Little is known regarding the clinical adoption of testing for carbamazepine, which may differ globally based on regional racial composition.

Abacavir/HLA-B*5701
This was the first label update based on strong evidence of clinical utility from a prospective randomized controlled trial, where patients were randomized to a HLA-B*5701 prescreening arm or to an arm without screening. Information on HLA-B*5701 was subsequently included in a boxed warning. The label recommends, but does not require, screening patients for the at-risk allele prior to initiating therapy. Clinical adoption has been relatively rapid and widespread, with positive reimbursement decisions from insurance companies, and recommendations for prescreening from HIV–AIDS professional associations.

Panitumamab/KRAS
& cetuximab/KRAS
This was the first label update that was based on a clear framework of principles for using prospective-retrospective biomarker data analysis,
for example, a mechanistic pathway hypothesis, a parallel high ascertainment rate (as high as 92% in some studies) and a sufficiently powered, prespecified statistical plan for using retrospective subset analysis of multiple clinical trial datasets. Clinical adoption was enabled when the American Society of Clinical Oncology (VA, USA) released a provisional clinical opinion on the use of KRAS testing before treatment with anti-EGFR monoclonal therapy in January 2009 (which preceded the label update). Screening for KRAS gene mutations was also added to the National Comprehensive Cancer Network’s clinical practice guidelines, and KRAS mutation analysis is considered medically necessary by several insurance companies. Clinical adoption of KRAS testing in metastatic colorectal cancer for patients for which an anti-EGFR monoclonal antibody therapy is being considered is widespread.

Clopidogrel/CYP2C19

This was the first label update based on synthesis from multiple epidemiological data sources, including academic cohort studies and subgroup analyses of cohorts from prospective, randomized clinical studies. Pharmacogenetic associations were mechanistically supported and strengthened by observational drug–drug (CYP2C19) interaction studies. FDA regulatory scientists worked with clopidogrel’s sponsor to generate specific data to answer outstanding questions regarding the pharmacogenetics of the active metabolite. In 2010, the label of clopidogrel was updated with a boxed warning to caution that poor metabolizers may not receive the full protection from heart attacks, stroke and cardiovascular death.

From these examples that we have discussed it is clear that an update of a label with genetic information by the FDA does not guarantee the adoption of genetic testing into the practice of medicine. The latter is too complex to expect that it would be that easy. However, assessment of risk–benefit is, and will continue to be, a central issue for the FDA, and labels represent a necessary vehicle to provide medically appropriate information on PGx. Patients and their healthcare providers need to be able to make informed decisions on whether or not genetic information is useful in a given clinical context.

Future trajectory

A quadriga is a chariot drawn by four horses abreast and was used centuries ago in Greek and Roman chariot racing. Today, we see quadrigas as symbols of commitment to innovation, a pioneering spirit through scientific activities, progress and victory. A modern quadriga, with the charioteer representing patient advocates (clinicians, translational scientists and patients themselves) and the chariot representing PGx, cannot be triumphant without the four enabling ‘horses’ moving in the same direction in the next 10 years. These four key areas for advancing PGx are: commitment to improving efficacy and safety of medicines, demonstration of clinical utility and clinician education, clear regulatory guidance, and rewards and reimbursement.

Commitment to improving the efficacy & safety of medicines

The pharmaceutical and biotechnology industries need to increase premarketing efforts to invest in targeted medicines for genetically or molecularly defined subsets of the disease population. Furthermore, as drug safety becomes a growing concern for regulatory agencies over the next decade, there will need to be a major effort to collect premarketing, postmarketing, DNA and safety phenotype data in order to develop associations and solutions. Sharing precompetitive and competitive safety data through consortia, such as the Serious Adverse Event Consortium [103], will have a profound effect on progress towards managing the risks of drug therapy. In addition, academic researchers must begin to fill science gaps in a way that can be used by therapeutics and diagnostics developers and regulators to make meaningful risk–benefit assessments. This will require research to be conducted in a more rigorous way than it has been to date. Specifically, when conducting ‘translational research’ in clinical and academic settings, researchers should be aware of the high evidentiary burden required to trigger investment by drug and diagnostic companies in a PGx discovery, and to convince public health agencies of the need for a particular intervention (e.g., changing a drug label) based on a research finding. Issues around study methodology, data and statistical analyses, and potential clinical relevance of findings should be carefully considered prior to hypothesis testing. The majority of PGx studies to date have been exploratory, making definitive conclusions regarding the public health importance of PGx associations difficult.

Demonstration of clinical utility & clinician education

The clinical utility of a genetic (i.e., diagnostic) test does not lie in the test itself but in the impact that the test result (i.e., information) has on a drug and/or dose selection decision, as
measured by either a reduction in the mortality or morbidity of a disease, or on an improvement in the safety of a medicine. In the next 10 years, the scientific community needs to develop a consensus framework for generating evidence on the clinical utility (and cost–effectiveness) of genetic tests. Credible prospective and retrospective clinical studies, with presupposed statistical plans for the collection and analysis of genomic data, can provide a useful framework for accepting or rejecting the adoption of genetic tests. Many clinical utility studies of genetic tests are most likely to be conducted in naturalistic settings (e.g., Medco [NJ, USA]–Mayo Clinic [MN, USA], Consumer Value Store [CVS; RI, USA]–Generation Health [NJ, USA]) after a medicine is marketed, since there is little incentive for a manufacturer to improve their benefit–risk profile following regulatory approval or after the drug loses patent protection. As we have previously articulated [5], the demonstration of systems-wide clinical utility should not be a prerequisite for clinical adoption of PGx in individual practices because utility may only be demonstrable in a given clinical context (e.g., chronic vs acute care; rural vs urban settings). Also of note, it is important to recognize that clinical utility of medical interventions are often only revealed after a decades long lag time [5]. Therefore, it may be inappropriate – maybe even unethical – to not utilize PGx data in clinical settings as evidence of utility accumulates in increments.

Clinicians (e.g., physicians and pharmacists) are the gate-keepers of the demand for personalized medicine. Yet, most clinicians today, understandably, have limited experience of how to use genomics in clinical practice, so adoption of genetic tests has been minimal, except in the subspecialties (e.g., cancer and HIV and AIDS), and a major gap exists between the ideal situation and reality. Significantly more effort by clinicians in taking individual ownership of PGx is needed, as well as a greater commitment from medical and pharmacy school faculty and healthcare providers of continuing education to teach clinicians how to use genomic knowledge to make more informed decisions regarding therapeutics for their patients.

■ Clear regulatory guidance

Regulatory models to deal with the personalized health space will continue to evolve incrementally. The FDA will make slow but steady progress in aligning regulatory guidance and policies with genomics and personalized medicines. In addition to continuing its VGDS program and updating labels with genomic information, the FDA expects to develop guidance for industry that will impact genomics in drug development over the next 5 years. These include: clinical pharmacogenomics guidance for early drug development, guidance related to premarket co-development of a drug and companion diagnostic, and guidance in dealing with enrichment strategies in clinical trials. The FDA also expects to clarify its regulatory authority in general, and those of its Center for Drug Evaluation and Research (MD, USA) and Center for Devices and Radiological Health (MD, USA), in the areas of laboratory-developed tests and multivariate gene assays in order to better enable informed investments in the development of diagnostic tests and personalized medicines.

■ Rewards & reimbursement

It is critical that government agencies, insurance companies, and other payers provide sufficient rewards for pharmaceutical, diagnostic and biotechnology companies to build a climate of continued investment in developing innovative medicines and diagnostic tests, and to positively change attitudes and behaviors with respect to adoption of PGx. Reimbursement systems need to change from a technology- and process-based framework (e.g., Diagnosis Related Groups that reward quantity) to a value-based framework (i.e., that rewards quality) to catalyze the adoption of genomic medicine. Drug development and healthcare in general is expensive (e.g., it costs almost US$1 billion to bring a molecule from discovery to market). Studies have reported that most drugs, on average, have an effectiveness rate of 50% and adverse drug reactions continue to be the fifth leading cause of death in the USA. Since prescription drugs are a significant driver of medical cost inflation, a reward and reimbursement system that rewards higher efficacy rates or lower adverse event rates through genetic diagnostic tests seems like a reasonable solution that stakeholders can embrace. The business concept is one of ‘value creation’, but it assumes that the healthcare system (i.e., physicians, payers, patients and providers) can come to an agreement on what genetic information is of value in solving clinical problems.

The federal government and the FDA have a track record of incentivizing or rewarding investments in new and/or needed medicines, as evidenced by such milestones as the Orphan Drug Act to promote therapeutics for rare diseases or
conditions, administering the fast track drug development programs (Section 506 of the FDA Modernization Act of 1997), accelerated approval of new drugs for serious or life-threatening diseases (21 Code of Federal Regulations Part 314, Subpart H), special protocol exemptions, treatment or emergency use of investigational new drugs, pediatric exclusivity (Section 505A of the Federal Food, Drug and Cosmetics Act), approvals based on evidence of effectiveness in animals (21 Code of Federal Regulations Part 314, subparts H and I), user fees for faster drug reviews (Prescription Drug User Fee Act, 1992) and the critical path initiative (e.g., defining a biomarker qualification process). Many of these incentives can be invoked as catalysts for the development of targeted drugs and genetic diagnostic tests, and it is unclear whether further governmental or regulatory incentives are needed, or if the opportunities listed above are sufficient.

The field of PGx and personalized medicine has grown modestly over the past 10 years. Some have grown impatient or have given up on this science owing to the perceived slow pace of its progress. So, what will the next 10 years hold? To answer this question, one looks back over the past 10 years – it wasn’t so long ago that we still used floppy discs, were conducting our first Google searches, and dropped our film off at a drug store to develop our pictures. In 2000, we would be years away from routinely ‘downloading’ all of our music, owning affordable high-definition televisions, and effortlessly navigating our cars to all points on the map using GPS technology. Genomic technologies have been equally substantial in our lives. One can obtain information on 1 million SNPs for comprehensive genetic predisposition testing for under US$500; the optimization of warfarin therapy is now possible through genetics for under US$250; tests are available for EGFR and KRAS mutations to guide cancer treatment; a gene-expression diagnostic test exists to look at a group of genes in a woman’s breast cancer tumor and tells her, personally, what the likelihood is that she will have cancer return or whether or not she would benefit from adding chemotherapy to her hormonal treatment. This is what genomics can do: give patients and their doctors choices that they otherwise would never have had. In our future, the quadriga has a rearview mirror. However, it is safe to say ‘don’t look in the rearview mirror’, except for a quick glance. We look ahead with optimism to the next 10 years, because the future will be an unrecognizable relative to the past in the field of genomics and personalized medicine.

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