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Application of Pharmacogenomics in Clinical Pharmacology

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Many factors can affect a patient's response to a drug. These include intrinsic factors such as age, gender, race/ethnicity, genetics, disease states, organ dysfunctions, and other physiological changes, including pregnancy, lactation, and extrinsic factors such as smoking, diet (food, juice, dietary supplements), and concomitant medications (ICH E5, 1998 and 2004). The interplay of genotypes of the enzymes, transporters and receptors, among other factors (such as concomitant medications and disease states), can affect the risk/benefit ratio for individual patients. This commentary discusses when the genomic information should be obtained during drug development and when it is to be assimilated into labeling and standards of care that can be used to "individualize" drug therapy and become one of the pillars of "personalized medicine."

Keywords Pharmacogenomics Application, Clinical Pharmacology

INTRODUCTION

Many factors can affect a patient's response to a drug. These include intrinsic factors such as age, gender, race/ethnicity, genetics, disease states, organ dysfunctions, and other physiological changes, including pregnancy, lactation, and extrinsic factors such as smoking, diet (food, juice, dietary supplements), and concomitant medications (ICH E5 1998 and 2004).

A recent review of post-approval dosage changes between 1980 and 1999 indicates that, of the evaluable drug products (n = 354), 21% had dosage changes (Cross 2002; see also comments in Temple RJ 2003). Many of these changes were based on new information that was obtained after the marketing approval of the drug products. These changes included dosing recommendations for specific populations, such as patients at various stages of renal or hepatic impairment, patients taking specific concomitant medications, or patients who are pregnant. The list included drugs that were subsequently withdrawn from the market. This study pointed out the importance of having accurate dosage recommendation for individuals with various intrinsic or extrinsic factors prior to marketing to reduce the risks of adverse drug reactions (ADR). ADRs, accounting for 5% of hospital admissions, were also experienced by 10% of hospitalized patients, have led to 700,000 injuries/deaths per year, and were estimated to be the 4th or the 6th leading cause of death in the United States for hospitalized patients (Lazarou 1998). Serious ADRs, caused by various factors, have contributed to market withdrawals. Table 1 lists drugs withdrawn from the US market in the past 7 years due to safety reasons (Huang 2004a).

DRUG METABOLIZING ENZYMES AND TRANSPORTERS

A recent analysis of 18 ADR studies conducted between 1995 and 2000 showed that 59% of drugs causing ADRs are metabolized by polymorphic enzymes while only 7–22% of other randomly selected drugs are substrates for polymorphic enzymes (Phillips 2001). These results suggest that doses based on individuals' metabolizing genotype may reduce the risk of ADRs of certain drugs. An updated list of CYP enzymes and literature references for in vitro or in vivo activities for various alleles is available on line (http://www.imm.ki.se/cypalleles/). In addition to polymorphism in metabolizing enzymes, there are polymorphisms in transporters, receptors, and other therapeutic targets. The extent to which the metabolizing enzyme genotypes affect pharmacokinetics and clinical responses is the subject of various recent reviews (Xie 2001; Evans 2003; Weinshilboum 2003; Pauli-Magnus 2004). There are several enzymes that are considered "valid" biomarkers based on the criteria described in a recently released guidance on pharmacogenomic data submission (FDA 2005a; http://www.fda.gov/cder/guidance/6400fnl.pdf). These valid biomarkers are defined as being measured in an analytical test system with well-established performance characteristics and for which there is evidence about the physiologic, toxicologic, pharmacologic, or clinical significance of the results (FDA 2005a). Table 2 includes several drug metabolizing enzymes considered valid biomarkers and summarizes the published correlation data between the metabolism genotypes and

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TABLE 1
Drugs withdrawn from the US market between 1997 and 2001 (Huang 2004a)

Year				
Withdrawn	Approval	Drug name#	Use	Risk
1997	1973	Fenfluramine (Pondimin)	Obesity	Heart valve abnormality
1997	1996	Dexfenfluramine (Redux)	Obesity	Heart valve abnormality
1998	1997	Mibefradil (Posicor)	High blood pressure/ Chronic stable angina	Drug-drug interactions Torsades de Pointes
1998	1997	Bromfenac (Duract)	NSAID	Acute liver failure
1998	1985	Terfenadine (Seldane/Seldane-D)	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1988	Astemizole (Hismanal)	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1997	Grepafloxacin (Raxar)	Antibiotics	Torsades de Pointes
2000	2000	Alosetron* (Lotronex)	Irritable bowel syndrome in women	Ischemic colitis; complications ofconstipation
2000	1993	Cisapride (Propulsid)	Heartburn	Torsades de Pointes Drug-drug interactions
2000	1997	Troglitazone (Rezulin)	Diabetes	Acute liver failure
2001	1997	Cerivastatin (Baycol)	Cholesterol lowering	Rhabdomyolysis Drug-drug interactions
2001	1999	Rapacuronium bromide (Raplon)	Anesthesia	Bronchospasm
2004	1999	Rofecoxib** (Vioxx)	NSAID (COX-2 inhibitor)	Cardiovascular risks

#Trade names are in parentheses.
*Reintroduced to the market in 2002 with use restricted to patients severely affected with irritable bowel syndrome.
**Updated information; subject of discussion at an FDA Advisory Committee meeting held in Bethesda, MD, February 14 to 18, 2005.

TABLE 2
DNA based biomarkers of enzyme activities considered as valid biomarkers (Huang 2005)

Enzyme	Model drugs	Outcome measures	Study results	Ref
CYP2C9	Warfarin	Maintenance dose Time to reach stable dosing	Patients with *2 and *3 maintained with lower doses and took longer time to reach stable dosing	Hill 2004; Peyvandi 2004; Higushi 2002
CYP2C19	Proton pump inhibitors	Plasma levels Gastric pH Gastroesophageal reflux disease cure rate	Higher in PM (20 mg) Higher dose (40 mg) showed no difference	Frurta 2004; Anderson 2005
CYP2D6	Codeine	Morphine formation Analgesic effects	Higher in EM	Eckhardt 1998
	Atomoxetine	Pharmacokinetic measure	PM higher AUC (10-fold)	FDA labeling
UGT1A1	Irinotecan	Grade 3/4 neutropenia	UGT1A1 7/7and 6/7 more frequent than 6/6	Rouits 2004; Innocenti 2004
		Pharmacokinetic parameters (AUC ratio of SN38G/SN38)	UGT1A1*28 and *6 with reduce ratios	Sai 2004; Iyers 2002
TPMT	6-MP	Dose-limiting hematopoietic toxicity	More in TPMT deficiency or heterozygosity	Evans 2004; Wein-shilboum 2001; Evans 2001

Note: UGT 1A1: uridine diphosphate glucuronosyl transferase 1A1; TPMT: thiopurine methyl transferase; SN-38: an active metabolite of ironotecan: SN-38G: a glucuronide metabolite of SN-38.

TABLE 3
DNA based biomarkers of enzyme or transporter activity currently considered as "exploratory" biomarkers (Huang 2005)

Enzyme/transporter	Model drugs	Outcome measures	Study results	Ref
CYP3A4	Testosterone	In vitro metabolism rate	*17 lower activity while *18 higher activity	Dai 2001
CYP3A5	Tacrolimus Cyclosporine	Pharmacokinetic parameters	*3 (non-expressor) associated with higher trough plasma concentrations	Haufroid 2004; Zheng 2004
CYP2B6	Efavirenz	Pharmacokinetic parameters	*6 homozygous associated with higher plasma concentrations	Tsuchiya 2004
CYP2C8	Repaglinide	Pharmacokinetic parameters	*3 associated with lower plasma concentrations	Niemi 2003
CYP2A6	Nicotine	Pharmacokinetic parameters	*7, *10 associated with higher nicotine and lower cotinine plasma concentrations	Xu 2002
ABCB1 (MDR1)	Digoxin	Pharmacokinetic parameters	TT homozygous C3435T associated with higher plasma concentrations	Hoffmeyer 2000
	Fexofenadine	Pharmacokinetic parameters	TT homozygous C3435 associated with lower plasma concentrations	Kim 2001
	Nelfinavir Efavirenz	Pharmacokinetic parameters & Immune recovery	TT homozygous C3435 associated with lower plasma concentrations, and greater rise in CD4 responses	Fellay 2002
	Antiepileptic drugs	Clinical responses	CC homozygous C3435 associated with drug-resistant epilepsy	Siddiqui 2003
ABCA1	Atorvastatin, Simvastatin, Pravastatin	LDL-cholesterol lowering	Higher adjusted mean change in certain HAP markers	Ruano 2003
OATP-C	Pravastatin	Pharmacokinetic parameters	*15 associated with lower clearance	Nishizato 2003

Note: ABCB1: ATP-binding cassette family (ABC) B1, multi-drug resistance.
(MDR1) a human gene that encodes P-glycoprotein; MRP: multi-drug resistance protein.
OATP-C: organic anion transporting peptide-C.

outcome measures (e.g., clinical efficacy, ADR, doses, PK and PD) for some model drugs.

Table 3 lists enzymes and transporters that are currently considered "exploratory" biomarkers. For some genes (e.g., *CYP3A4*), the correlation between certain genotypes and enzyme or transporter activities was observed in vitro only. For others (e.g., *ABCB1*), contradictory data have been published for different drugs and the correlation between SNP genotype or haplotype and the phenotype (PK parameters, other response measures) will need to be further defined.

Although the cases listed in Tables 2–3 are mostly from monogenic studies, many drugs display polygenic traits. The interplay of genotypes of the enzymes, transporters, and receptors, among other factors (such as concomitant medications and disease states), can affect the risk/benefit ratio for individual patients (Evans 2004; Weinshilbum 2004) and need to be considered when evaluating varied results from many genotyping studies with small number of subjects. But accounting for variability using even one gene of the polygenic traits may improve the benefit/risk ratio without having full knowledge of other genes.

PRE-APPROVAL EVALUATION

In order to optimize drug dosing and reduce adverse event rates, it is critical that exposure be available for the health care providers and patients. As part of the "good review practices" during the regulatory review of the clinical pharmacology and biopharmaceutics data in an IND or NDA submission, key dose, pharmacokinetic (PK), pharmacodynamic (PD) parameters, and clinical outcomes, and their variability in various population groups are reviewed in an integrated approach (CDER 2004). As an example, Figure 1 depicts the changes in systemic exposure in various population groups of a recently approved drug, atomoxetine (FDA 2002). The clinical significance of these PK changes depends on the comparative concentration-response relationships for both efficacy and toxicity (CDER 2003b). Table 4

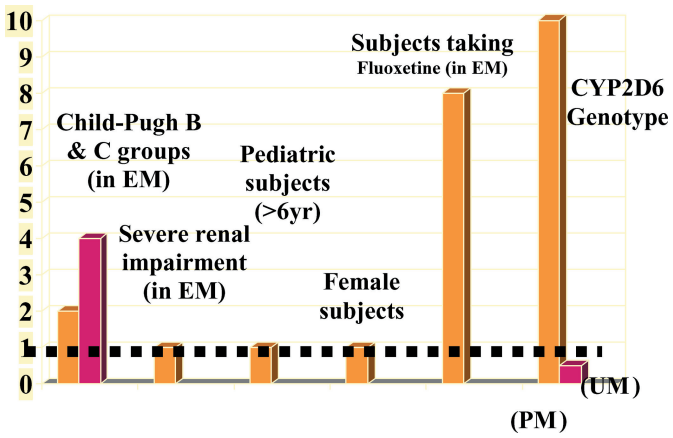

FIG. 1. Fold-change in systemic exposure (area under the concentration-time curve) of atomoxetine in specific population groups as compared to a control group (the control group consists of subjects with normal hepatic function, subjects with normal renal function, adults, male subjects, subjects not taking concomitant drugs, and subjects with EM status [extensive metabolizer of CYP2D6], respectively); data from (FDA 2002).

shows the corresponding labeling recommendations for this drug in specific patient groups (FDA labeling). Atomoxetine is metabolized by CYP2D6, a polymorphic enzyme. Using a learn-confirm paradigm, the pharmaceutical company collected, in addition to PK data, the efficacy and safety data in patients identified retrospectively as extensive metabolizers (EM) of CYP2D6 and compared these data with those identified as poor metabolizers (PM) of CYP2D6 and the results were stated in the label. Many of the studies evaluating the effect of various intrinsic and extrinsic factors on PK of atomoxetine were conducted in EMs of CYP2D6. With the exclusion of PM subjects, the evaluation of changes in PK in patients with hepatic impairment or in patients taking CYP2D6 inhibitors will not be confounded by the patients' intrinsic CYP2D6 enzyme status. However, it remains uncertain as to what the effect of these factors would be in PMs although mechanistically it would seem that effects would be greater in EMs than PMs.

POST-APPROVAL EVALUATION

As science and technology advance and additional post-marketing adverse event information in specific population groups becomes available post-approval, the information will be included in the labeling, as appropriate. Several recent examples include the addition of the genetic information to the labeling of 6-mercaptopurine (PURINENTHOL), azathioprine (IMURAN), and irinotecan (CAMPTOSAR). There are hundreds of products whose labels are revised each year.

6-MERCAPTOPURINE AND AZATHIOPRINE

Azathioprine is metabolized to 6-mercaptopurine (6-MP). Patients with low or absent TPMT activity are at an increased

TABLE 4
Atomoxetine (STRATTERA®) label recommendations in patients defined by various intrinsic and extrinsic factors; information adapted from (FDA 2002)

Extrinsic or intrinsic factors	Atomoxetine AUC fold-change	Atomoxetine Cmax fold-change	Atomoxetine labeling
			Approved dosing: 0.5 mg/kg initially up to 1.2 mg/kg (no more than 1.4 mg/kg/day or 100 mg, whichever is less)
Hepatic* (Child-Pugh C)	4	—	Reduced to 25% of the normal dose
Hepatic* (Child-Pugh B)	2	—	Reduced to 50% of the normal dose
Renal*	1		No recommended dose change
Pediatric (>6YO)	Similar		No recommended dose change
Gender (female)	1		No recommended dose change
Co-administration with fluoxetine, paroxetine, quinidine*	6–8	3–4	Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine. In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine
CYP2D6 genotype	10	5	Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA

*Studies conducted in EM of CYP2D6; "renal": subjects with end-stage renal disease; "pediatric": adolescents and children under 6 years old.

risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of 6-MP (Otterness 1997; McLeod 2000). Both Purinenthol and Imuran product labels have been recently updated (July 2004 and July 2005, respectively, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda) to include the following information.

"6-MP undergoes two major inactivation routes. One is thiol methylation, which is catalyzed by the enzyme thiopurine S-methyltransferase (TPMT), to form the inactive metabolite methyl-6-MP (6-MeMP). TPMT activity is controlled by a genetic polymorphism. For Caucasians and African Americans, approximately 10% of the population inherit one non-functional TPMT allele (heterozygous) conferring intermediate TPMT activity, and 0.3% inherit two TPMT non-functional alleles (homozygous) for low or absent TPMT activity. Non-functional alleles are less common in Asians. TPMT activity correlates inversely with 6-TGN levels in erythrocytes and presumably other hematopoietic tissues, since these cells have negligible xanthine oxidase (involved in the other inactivation pathway) activities, leaving TPMT methylation as the only inactivation pathway. Patients with intermediate TPMT activity may be at increased risk of myelotoxicity if receiving conventional doses of 6-MP or IMURAN. Patients with low or absent TPMT activity are at an increased risk of developing severe, life-threatening myelotoxicity if receiving conventional doses of 6-MP or IMURAN. TPMT genotyping or phenotyping (red blood cell TPMT activity) can help identify patients who are at an increased risk for developing IMURAN toxicity."

Irinotecan

Irinotecan is hydrolyzed by carboxylesterases to SN-38, the active form. SN-38 is further metabolized by glucuronosyltransferases, primarily by UGT1A1 (Thorn 2005). UGT1A1*28 is a valid biomarker for decreased UGT1A1 activity resulting in an increased risk of irinotecan toxicity (FDA 2004; Andersson 2005, and references therein). The Camptosar product labeling has been recently updated (July 2005) to include the following information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

*"The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients who were homozygous for UGT1A1*28 had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (See WARNINGS and DOSAGE AND ADMINISTRATION)."*

The drug label further recommends a reduced starting dose of patients who are homozygous for UGT1A1*28 alleles.

Both the above new label information attempts to convey to the health care providers and patients that the genotyping information is critical in the safe and effective use of these therapies.

Type of Genomic Data that Qualifies as Valid Biomarkers

The type of genomic data (e.g., which alleles, what genotypes) that needs to be evaluated, and when, is one of the critical issues in drug development and regulatory review (Huang 2004c). In some cases, consideration of racial/ethnic differences in the distribution of various alleles with no or reduced metabolic activity in the evaluation of dose-response relationships is important. For example, Table 5 lists the recommended polymorphic alleles to measure in specific population groups for CYP2C9, CYP2C19, CYP2D6 and UGT1A1 based on discussions at a workshop (FDA workshop 2004; Andersson 2004, 2005; Flockhart 2004; Huang 2004; Milos 2004; Ratain 2004).

DRUG INTERACTIONS

While pharmacogenetics of metabolizing enzymes can affect patients' drug exposure and subsequently response to treatment, concomitant drug or dietary supplement administration is another important factor that can cause altered drug response. Recent studies have shown that the extent of drug interactions may be impacted by genotypes of the interacting drugs. Table 5 lists some examples (Huang 2005). This type of information has started to appear in the product label. For example, in contrast to the warning for EMs of CYP2D6 that "Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine," no similar warnings for PM of CYP2D6 are in the label. The labeling indicates that "In vitro studies suggest that co-administration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine" and no dosage adjustments in PM was recommended. The problem is that in order to use this information, the provider needs to have access to genotype information which at this time may not be readily accessible for general practitionsers.

Voluntary versus Required Submissions

Whether certain type of pharmacogenomic data need to be submitted to the Agency as required by regulation for review is discussed in a FDA guidance (FDA 2005; http://www.fda.gov/cder/guidance/6400fnl.pdf) and discussed in workshop reports (Salerno 2004a, 2004b; Leighton 2004; Ruano 2004a; Trepicchio 2004). The following cases highlight scenarios in drug development and illustrate the basis for submitting pharmacogenomic information to the FDA as voluntary or required data submissions.

Scenario 1

A sponsor conducts a phase 3 clinical trial of a NME in patients with the target indication. The NME is metabolized

TABLE 5
Summary of recommended polymorphic alleles of specific metabolizing biomarkers to measure in specific population groups (adapted from Andersson 2005)

Enzymes	Basic alleles to measure in all population groups	Additional alleles relevant to specific population groups		
		Caucasians[1]	African Americans[1]	Asian Americans[1]
CYP2C9	*2, *3		*5, *6	
CYP2C19	*2, *3	*4, *5, *6		
CYP2D6	*3, *4, *5, *6, *2 × N	*10 (*41)[2]	*17	*10 (*21) [2]
UGT1A1	*28		(*60)[2]	(*6)[2]

[1]Additional alleles to measure in this specific population group.
[2]Possible additional alleles to measure in this specific population group.

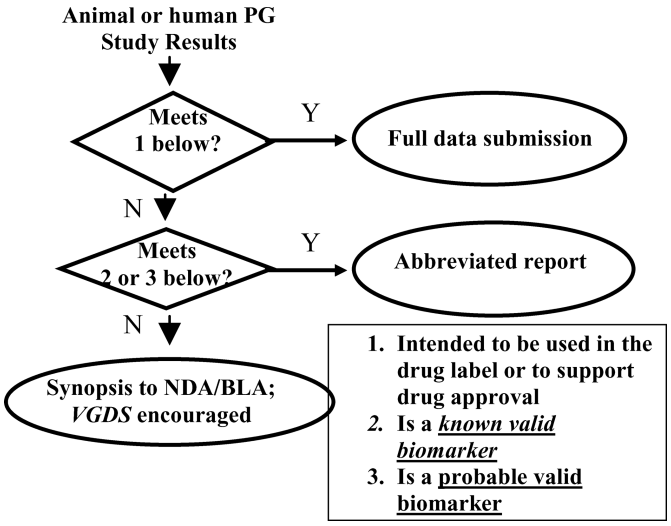

FIG. 2. Flow chart indicating whether the genomic data are required to be submitted as full or abbreviated reports or synopsis with recommended voluntary submissions for NDA and BLA applications.

primarily by CYP2D6 to an active metabolite equipotent to the parent molecule. The sponsor genotypes a randomly selected subset of the patients for their CYP2D6 alleles in order to explore the association between genotype, drug dosing and clinical outcome. The results show minor differences in clinical outcomes among the genotypes. The information is included in the proposed labeling in the NDA submission.

Type of Submission and Rationale: Full report (NDA). The sponsor will use the test results in the drug label (see Fig. 2).

Scenario 2

A sponsor conducts a phase 3 clinical trial of a NME in patients with the target indication. The NME is metabolized primarily by CYP2D6 to an active metabolite equipotent to the parent molecule. After the trial is completed, the sponsor genotypes a randomly selected subset of the patients for their CYP2D6 alleles in order to explore the association between genotype and plasma clearance values. The sponsor has not proposed to include the results in the labeling.

Type of Submission and Rationale: Abbreviated report (IND or NDA/BLA). Although the test results may not be used in decision-making about drug dosing in the drug label, CYP2D6 is a known valid biomarker, therefore, the test results need to be submitted as an abbreviated report.

TABLE 6
The effect of genotypes on the extent of drug interactions (Huang 2005)

Substrate (enzyme)	Inhibitor or inducer	Outcome (changes in plasma AUC or concentrations of substrates)	Ref
Atomoxetine (CYP2D6)	Fluoxetine, paroxetine	AUC increase 6–8 fold in EM; no change in PM expected	FDA labeling
Metoprolol (CYP2D6)	Diphenhydramine	Higher inhibition in EM vs. PM (fold vs. fold)	Hamelin 2000
Tamoxifen (CYP2D6)	Paroxetine	Greater reduction in plasma levels of endoxifen (active metabolite of tamoxifen formed via CYP2D6) in homozygous EM as compared to patients with at least one variant allele	Stearns 2003
Diazepam (CYP2C19)	Omeprazole	No inhibition in PM	Andersson 1990
Omeprazole (CYP2C19)	Fluvoxamine	AUC increased 3–6 fold in EM; no changes in PM	Yasui-Furukori 2004
Omeprazole (CYP2C19)	Gingko Bloba	Higher induction in EM	Yin 2004 or 5

Check: Yin OQP, Tomlinson B, Waye MMY, Chow AHL, Chow MSS, Pharmacogenetics and herb–drug interactions: experience with Ginkgo biloba and omeprazole, Pharmacogenetics, in press.

Scenario 3

A sponsor conducts a drug interaction study in healthy volunteers of their NME, a CYP3A substrate, co-administered with ketoconazole as an enzyme inhibitor. Subsequent to the study, the subjects are genotyped for their CYP3A5 alleles to determine the relative contribution of this polymorphism to inter-individual variability in AUC.

Type of Submission and Rationale: For submissions under IND, these data would be eligible for a VGDS. For submissions under NDA/BLA, these data would be required to be submitted as a synopsis and a voluntary genomic data submission (VGDS) is encouraged. The test results are not being used in decision-making or scientific arguments or in the drug label or as part of the scientific database. In addition, polymorphism of CYP3A5 is not yet a probable or known valid biomarker. The information on this genotype is considered to be exploratory.

Examples of Recent Voluntary Genomic Data Submissions (VGDS)

Recent VGDS submissions have included both clinical as well as preclinical data. The FDA has had a chance to discuss with sponsors of these submissions of pharmacogenomic data the significance of the data and how it is associated with both clinical efficacy as well as risk. These VGDS submissions have included analysis of data associated with gene expression changes as well as genotyping. Reviewers have worked on the analysis of raw DNA chip hybridization data submitted as part of several recent VGDS submissions. The analysis of these data has helped both with training in pharmacogenomics for reviewers as well as in the development of expertise at a level closely linked to the review process that will help prepare reviewers for future industry submissions and a seamless inclusion of pharmacogenomic data in regulatory use. Hybridization data analysis has made use of ArrayTrack for statistical analyses and of biological pathway analysis tools such as Ingenuity for the biological interpretation of the data. Reviewers have both been able to reconstruct analyses for results reported by sponsors as well as to add value to the original biological interpretation of the data with a more in-depth analysis of the data. The downstream value of this work is to assure that there will be no delays in future genomic reviews because FDA is unfamiliar with these experiments and data.

LABELING IMPLICATIONS

Labeling for drug products in the US needs to be in the format per the Code of Federal Regulations (21 CFR 201.56). In a final rule of physician labeling, new content and format requirements are described for the labeling of human prescription drug and biological products (FR notice 2006: http://www.fda.gov/cder/regulatory/physLabel/default.htm). Pharmacogenomic data and related information can be described in the following sections as appropriate: "Indications and Usage," "Dosage and Administration," "Contraindications," "Warnings and Precautions," "Adverse Reactions," or "Clinical Pharmacology," "Drug Interactions," or "Use in Specific Populations" (FDA Advisory Committee Meeting 2005). When different pharmacogenomic subgroups show clinically relevant responses (in safety, efficacy, pharmacokinetic, or pharmacodynamic profiles, or dose requirements), the information may be included in the labeling. Depending on the risk/benefit, the information may be placed in different sections of the labeling. When the genomic test must be conducted prior to dosing (for patient selection and/or dose selection), it may be stated in the "Indications and Usage" section (e.g., HERCEPTIN) with relevant information placed in other sections such as "Clinical Studies," (e.g., "HER2 testing," "HER2 detection"). When dose reduction may be important for specific genotypes, the information can be placed in "Dosage and Administration" and "Warnings" sections (e.g., PURINETHOL) with relevant information in other sections such as "Clinical Pharmacology," "Laboratory test," and "Adverse Reactions." When the adverse events are serious (e.g., Torsades de Pointes) and appropriate dose adjustments cannot be determined, the information may be included in "Contraindications" (e.g., thioridazine) and relevant information placed in other sections as appropriate. When there are no serious adverse events, however, the genotype information could be helpful in reducing less serious adverse events by dosing adjustments, the information may be placed in various sections, such as "Clinical Pharmacology," "Drug Interactions," "Adverse Events," "Laboratory test," "Special Populations," etc. (e.g., STRATTERA)

CONCLUSION

The two-fold mission of the U.S. Food and Drug Administration (FDA 2004) is to advance public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable (FDA 2004) and to assure that approved products are relatively safe in terms of risk and effective. As part of the FDA's strategic plan (FDA 2003), the Agency is developing standards to handle emerging technologies such as genomics, in order to provide efficient and rapid translation of new scientific developments and breakthroughs into applications that enable the development of safe and effective medical products. Pharmacogenomics is one of the fields that the FDA seems to have a large potential to influence the safety and efficacy of such new products, i.e. by translating the research on genetic variability into regulatory actions such as drug labels. This is only the first step. Ultimately, this knowledge must be assimilated into standards of care that can be used to "individualize" drug therapy and become one of the pillars of "personalized medicine." To clarify the FDA's current thinking and provide guidance to industry about what type of pharmacogenomic information the Agency expects to receive, a final "Guidance for Industry: Pharmacogenomic Data Submissions" has been published (http://www.fda.gov/cder/guidance/6400fnl.pdf), together with two companion documents and a newly created website for Genomics at the FDA (www.fda.gov/cder/genomics). The guidance is intended to clarify what type of genomic information needs to be submitted to the Agency and when, and it

offers a new submission path called "Voluntary Genomic Data Submission (VGDS)" to encourage sponsors that are using pharmacogenomics in exploratory research to submit such information for early discussion with the FDA, but without regulatory implications. In addition, various guidance documents on the development of pharmacogenomic testing have been published (FDA 2003, 2004, 2005). Another workshop (DIA 2004) was held in July 2004 to identify issues in the development of these combination products and a concept paper was published (FDA 2005b). It is important to note that despite significant scientific progress, a critical factor in bringing pharmacogenomics "from the bench to the bedside" is educating many different health care professionals about the logistics and benefits of using genetic and genomic information to individualize drug therapy. This has not reached a level of critical mass yet by which translation of this knowledge can be measured by its use in the clinic. This is not unexpected given the relatively short time for pharmacgogenomics. Consequently, significantly more effort is needed to not only ensure good science, but also to invest in educational programs that inform physicians, pharmacists, clinical chemists, laboratory directors, third party providers and patients about the potential of this new and exciting field to improve public health. The FDA has made a commitment and investment in pharmacogenomics with people, time and technology, and with increasing knowledge and the availability of novel tools, the FDA will continue to foster genomic-based research and drug development, and the translation of the resulting scientific data to clinical practice (Frueh 2004, 2005; Goodsaid 2006, in press; Huang 2005; Lesko 2004).

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