Is This the Drug or Dose for You?: Impact and Consideration of Ethnic Factors in Global Drug Development, Regulatory Review, and Clinical Practice

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Differences in response to medical products have been observed in racially and ethnically distinct subgroups of the US population.[1,2] These differences may be attributable to intrinsic ethnic factors (e.g., genetics, metabolism, and elimination), extrinsic ethnic factors that are associated with environment and culture (e.g., medical practice, diet, use of alcohol, and concomitant drug use), or interactions among these factors (**Figure 1**).[3] Behind these "ethnic" factors, of course, are individual differences that may be more common in particular subgroups but are generally present in all groups, albeit with different frequencies. Although subgroup differences are of great therapeutic and scientific interest, the ultimate goal is to understand these differences so that treatments can be truly individualized.

In order to foster a better understanding of how medical products might differ in their performance in individual patients, the US Food and Drug Administration (FDA) requires tabulation in New Drug Applications (NDAs) of the numbers of participants in clinical trials by age group, gender, and race, as well as any characterization of the safety, effectiveness, and dose-exposure results of treatment in these same subgroups[4] and, when appropriate, in other subgroups of the population of patients, such as patients with hepatic or renal failure, patients with different levels of severity of the disease, and patients with particular metabolic characteristics, such as CYP2D6 poor metabolizers. Sponsors are also encouraged to characterize the metabolism

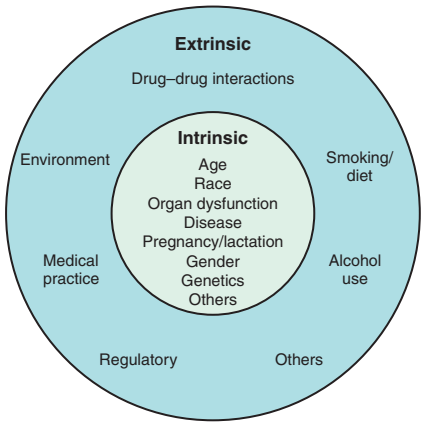

Figure 1 Intrinsic and extrinsic ethnic factors affecting exposure and drug response and risk–benefit assessment in different populations and regions. (Adapted from ref. 3.)

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and transport of drugs, assess potential drug–drug interactions, study the pharmacokinetic (PK) effects of renal and hepatic dysfunction, and utilize population PK approaches to recognize unanticipated PK differences.[5,6] Accordingly, during regulatory review of clinical pharmacology data in Investigational New Drug applications and NDAs, questions about how intrinsic and extrinsic factors might have influenced dose exposure and exposure response and the impact of differences in exposure on efficacy or safety responses are routinely asked.[7]

Dose–response and exposure–response relationships

Regulators have long stressed the importance of assessing a drug's dose–response relationships and, if possible, exposure–response relationships for both safety and effectiveness during drug development.[8] The recommended study design is the randomized fixed-dose, dose–response study, a design with many advantages but one limitation: it gives information only about the entire study group and possibly about certain subsets (age, race, gender) that are defined at baseline and are of interest in regulation (21 CFR 314.50) but does not yield any individual dose–response data because each patient receives only a single dose. Titration designs expose patients to multiple doses but confound dose and time of exposure, and only in the forced-titration design do the treatment groups for each dose remain unchanged. A randomized, multiple-dose, crossover dose–response study could provide both group and individual data, but such studies are very uncommon. What this means is that we have reasonably good data on group safety and effectiveness dose–response relationships but cannot determine whether individuals differ in important ways in their responses.

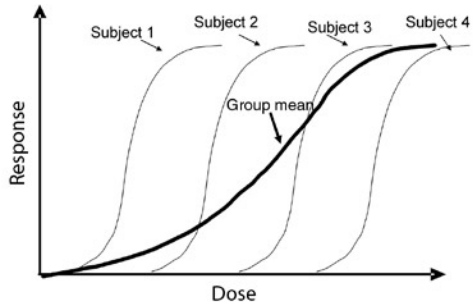

Figure 2 Possible dose–response curves: group mean vs. individual curves.

In a typical randomized fixed-dose, dose–response study, when we see the typical group mean dose–response curve (**Figure 2**), we cannot tell whether all patients have the same dose response or the group curve is made up of individual responses that are very different. If such differences were predicted by a demographic feature, they might be detected by standard subset analyses, but if they reflect unrecognized genetic or physiologic pharmacodynamic (PD) differences, they would not. This difficulty arises because most clinical responses in a trial are a mixture of responses to the drug and spontaneous change, so the effect of the drug can be detected only by comparing results in the two large treatment groups, i.e., drug and placebo.

An exception to this difficulty in interpreting individual responses is drug concentration, which can be known precisely for each individual in a trial, not just for the group. Differences among individuals in pharmacokinetics can therefore be readily identified and their causes elucidated, and the ability to do this has grown dramatically. As a result, we can make use of clinical measures to establish the dose response for the group, then use modeling and simulation, together with "individual" blood concentrations, to describe an overall

concentration–response relationship. It should be appreciated, however, that when we do this, we are developing a "group" concentration–response relationship and presume a similar concentration–response relationship for all individuals. Without multiple doses/concentrations, we cannot determine individual concentration–response relationships.

When an optimal dose for a whole group has been selected on the basis of the assessment of the overall risk-to-benefit ratio, it is relatively straightforward to determine dosing adjustments needed for patients with specific intrinsic and extrinsic factors that alter their pharmacokinetics, because we know the systemic exposure (concentration)–response (C/R) relationships. **Figure 3** shows the kind of dosage adjustments we make for various patient population groups based on the known alterations these groups have in systemic exposure, as estimated by either the area under the plasma concentration–time curve or, when appropriate, other parameters, such as maximum plasma concentration (C_{max}). These alterations include differences based on renal or hepatic function, metabolic enzyme (CYP2D6) or transport differences, or concomitant therapy. Fundamentally, we adjust doses based on these PK differences to give people with different pharmacokinetics the same blood concentrations as everyone else. This presumes that everyone's concentration–response relationship for PD and clinical measures is the same. Of course, we know that C/R relationships can differ among individuals, but such individual differences in C/R for PD and clinical responses are harder to measure than differences in drug concentrations.

It is clear, however, that the next step in determining individual dose–response relationships, beyond adjusting for individual PK differences, will be

Group	Ethnic factor	Fold change in exposure (AUC)	Initial dose (mg)	Daily dose (mg)
1	Control	1-fold	10–20	5–40
2	Hepatic impairment	1.1-fold (mild) 1.2-fold (moderate)	10–20 10–20	5–40 5–40
3	Renal impairment	1-fold (mild) 1-fold (moderate) 3-fold (severe)	10–20 10–20 5	5–40 5–40 ≤10
4	Race	2-fold (Asians)	5	5–20
5	Cyclosporine	7-fold		5
6	Gemfibrozil	1.9-fold		10
7	Lopinavir/ ritonavir	5-fold		10

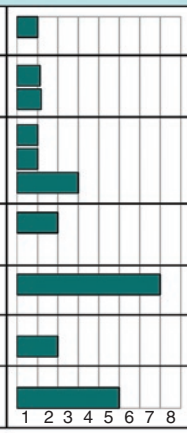

Figure 3 Comparative systemic exposure and corresponding starting (and maintenance) dose recommendation in subgroups with various patient factors: young healthy male subjects (control); patients with various degrees of hepatic impairment based on the Child–Pugh scores, subgroups A or B (hepatic); patients with varying degrees of renal impairment (creatinine clearance of 50–80, 30–50, <30 mL/min, or <30 mL/min with hemodialysis (renal); Asians compared with Caucasians (race); individuals taking concomitant medications such as cyclosporine, gemfibrozil, or lopinavir/ritonavir. (Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.)

detecting individual (or particular group) C/R relationships. It will almost certainly be biomarkers, rather than final clinical end points, that will be best able to define the different C/R relationships among individuals. Differences can be based on receptor genotypes or phenotypes, enzyme expression profiles, or metabolomic and proteomic differences, all of which are usually determined by a patient's intrinsic factors but can be related to extrinsic factors (e.g., blood pressure can become more renin-dependent and responsive to drugs inhibiting the renin–angiotensin system if diuretics are given). It has become very clear that effects such as tumor response, overall survival, and progression-free survival in oncology can vary based on genetic or tumor receptor differences. Other measures, such as cholesterol response, changes in international normalized ratio (INR) and blood pressure, blood pressure response, and QT prolongation, can be different in different individuals, reflecting genetic characteristics, physiologic differences, receptor activity, and other factors. It should be noted that PD differences may be manifested as differences in maximum response or as shifts in the C/R curve but with similar maximum effect. Ongoing efforts and successes in integrating use of biomarkers into drug development, regulatory review, and clinical practice have recently been described.[9,10]

Intrinsic factors

Genetics and race. In this issue, several articles[11–14] consider how a patient's genetics can affect the clinical outcome of warfarin treatment. It is of interest that these differences are both PK- (metabolic) and PD-based. Studies have shown that the usual methods for choosing warfarin dose give less than optimal results, with delays in reaching the desired INR and too frequent overshooting of the goal INR. A study by Gage *et al.*,[13] for example, showed poor prediction of dose based on clinical data (e.g., age and weight) alone; much better prediction was attained with additional incorporation of genetic information on CYP2C9, which metabolizes the more active form (S-) of warfarin, and VKORC1, the enzyme responsible for vitamin K metabolism and the target for warfarin action. There is some debate about whether superior INR results alone should be a basis for changing medical practice or whether there is a need for data from randomized prospective clinical trials using "hard" clinical outcomes, such as prevention of major bleeding or thromboembolic stroke. It is long-standing practice, however, to use INR as a surrogate for appropriate anticoagulation, and there are considerable data showing that INRs below 2 lead to more strokes, whereas INRs above 4 lead to excess bleeding. The FDA relied on publications using INR as an end point in both prospective and retrospective studies to support its recent revision of labeling of warfarin to include both CYP2C9 and VKORC1 genetic information in the "Dosage and Administration" section.[15]

Large-scale, prospectively designed outcome studies may not be essential when there is a clear mechanistic basis for an association between a genetic or proteomic difference and a highly predictive marker, particularly when the marker reflects the fundamental target effect of the drug. Sometimes past practice corroborates the linkage between the genetic marker and outcome. For example, recent data showing a higher prevalence of a warfarin-sensitive genotype of VKORC1 in Asians than in Caucasians is consistent with the past FDA labeling of warfarin and practices in some Asian countries based on evidence that Asians need a lower starting dose than Caucasians

do. Differences in prevalence of poor metabolizers of CYP2D6 or CYP2C9 are well described and consequential and can be assessed without outcome trials. On the other hand, prospectively designed studies to support dosage modifications may be critical when the mechanistic consequences of genetic differences are less clear.

Age (pediatrics) and race. Evaluation of pediatric studies conducted for 108 products between 1998 and 2005 in response to the FDA's written requests indicated that unique pediatric dosing is often necessary, reflecting growth and maturational stages of pediatric patients, and that pediatric dosing should not be determined by simply applying weight-based calculations to the adult dose.[16] Apart from these largely pharmacokinetics-based differences, a study in the current issue[17] suggests differential effectiveness in antihypertensives, particularly angiotensin-converting enzyme inhibitors, between black and white pediatric patients, reflecting a similar trend seen in adults. This example, along with the warfarin data discussed above, indicates the need not only to evaluate effects of individual ethnic factors on drug response but also to consider interactions between intrinsic factors, such as race and genetics or age and race.

Table 1 lists examples of currently marketed drugs with labeling that includes specific race or genetic information intended to facilitate the optimal use of medications in various population groups. Some of the observed racial differences may be explained by the genetic differences listed in labeling (e.g., warfarin and carbamazepine). Possible mechanisms for others either have not yet been included in labeling (e.g., rosuvastatin and tacrolimus) or are as yet unknown (e.g., isosorbide dinitrate–hydralazine, which is effective in heart failure in black patients).

Extrinsic factors

Drug–drug interactions (and genetics). Inappropriate use of concomitant drug products is a significant factor in adverse drug reactions in hospitalized patients. The evaluation of cytochrome P-450–based drug interactions has become routine, and methods of evaluation are being standardized. The FDA has provided recommendations on the study design, data analysis, and labeling language.[5,6] Current recommendations include discussions of the possibility of a different extent of drug interactions between population groups with different genotypes of the enzymes being modulated by concomitant drug administration; for example, poor metabolizers of CYP2D6, more common among Caucasians, have no or low risk of interactions with CYP2D6-inhibiting drugs (see, e.g., atomoxetine in **Table 1**). As transporter-based interactions are being increasingly uncovered and evaluated, a workshop supported by the FDA Critical Path Initiative has been planned, and the resulting white paper will discuss state-of-the art methods of evaluation, the impact of transporters in drug development (drug interactions and drug toxicity), and future directions (http://www.fda.gov/Cder/drug/drugInteractions/default.htm). Several articles in this issue show differences in the ethnic distribution of various genotypes of genes encoding for metabolizing enzymes and transporters.[2,18–20] Using probe substrates, it has been shown that concentrations of drugs metabolized by polymorphic enzymes (CYP2C9, CYP2C19, and CYP2D6) are influenced more by the genetics of these metabolizing enzymes than by ethnicity or region.[18]

Table 1 Examples of recent FDA drug product labeling that included ethnicity or genetic information

Therapeutic area	Drug products: generic (brand) names	Ethnicity information	Genetics information
Cardiorenal	Isosorbide dinitrate–hydralazine (BiDil)	Indicated for self-identified blacks	
	Angiotensin II antagonists and ACE inhibitors	Smaller effects in blacks[a]	
Metabolic	Rosuvastatin (Crestor)	Lower dose for Asians	
Transplant	Azathioprine (Imuran)		Dose adjustments for TPMT variants
	Tacrolimus (Protopic)	Higher dose for blacks	
Oncology	Trastuzumab (Herceptin)		Indicated for HER2 overexpression
	Irinotecan (Camptosar)		Dose reduction for *UGT1A1*28*
	6-Mercaptopurine (Purinethol)		Dose adjustments for TPMT variants
	Erlotinib (Tarceva)		Different survival and tumor response in EGFR-positive and -negative patients reported
Antiviral	Maraviroc (Selzentry)		Indicated for CCR5-positive patients
	Oseltamivir (Tamiflu)	Neuropsychiatric events mostly reported in Japan	
	Abacavir (Ziagen)		Boxed warning for HLA-B*5701 allele
Pain	Codeine		Warnings for nursing mothers that CYP2D6 UM metabolized codeine to morphine more rapidly and completely[b]
Hematology	Warfarin (Coumadin)	Lower dose for Asians	Lower initial dose for CYP2C9- and VKORC1-sensitive variants
Psychopharmacological	Thioridazine (Mellaril)		Contraindication for CYP2D6 PM
	Atomoxetine (Strattera)		Dosage adjustments for CYP2D6 PM; no drug interactions with strong CYP2D6 inhibitors expected for PM
Neuropharmacological	Carbamazepine (Tegretol)	Box warning for Asians with variant alleles of *HLA-B*1502*	Box warning for Asians with variant alleles of *HLA-B*1502*

ACE, angiotensin-converting enzyme; CCR5, chemokine (C-C motif) receptor 5; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; PM, poor metabolizer; TPMT, thiopurine methyl transferase; UGT, uridine diphosphate glucuronosyl transferase; UM, ultra-rapid metabolizer; VKORC, vitamin K reductase complex. Data from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.
[a]A general statement in the candesartan (Atacand) labeling. [b]http://www.fda.gov/cder/drug/infopage/codeine/default.htm.

Medical practice/regulatory requirements. Differences in drug approvals and in approved doses and dosing regimens in different regions of the world have been observed. A recent survey of the most frequently prescribed drugs in various regions indicated a trend toward lower approved doses in Japan. Although most approved doses are similar in the United Kingdom and the United States, there have been exceptions.[21] For example, the approved doses for candesartan, an angiotensin II receptor antagonist used for hypertension, are 4–8 mg (maximum 12 mg) in Japan, 4–16 mg in the United Kingdom, and 8–32 mg in the United States. Another example is ciprofloxacin, for which the doses for intravenous injection are 600 mg in Japan, 200–800 mg in the United Kingdom, and 400–1200 mg in the United States. We do not know whether these differences relate to intrinsic factors (e.g., body weight or genetics) or to differences in the regulatory environment (e.g., differing interpretation of risk–benefit balance among the countries).

For example, before a drug is approved in Japan, the Japanese Regulatory Agency seems to require additional data in the Japanese population[22] on doses lower than those studied in other countries, apparently reflecting either a different experience or a different attitude toward dose.

Unfinished work (future directions)

Development of targeted ("individualized") therapy will depend greatly on increased knowledge of all the factors that affect exposure, an area that has seen vast growth in knowledge and approaches, as well as the factors that alter ability to respond, the size of the response, and the C/R relationship. Because these differences depend on discerning individual PD and clinical responses, their evaluation is a significant challenge. Greater availability of state-of-the-art genetics and genomics tools has helped in their development, and it is expected that novel biomarkers that can better predict individual responses will help further.

A recent SACGHS report[23] indicated that pharmacogenomics can be used as a tool for personalizing health care on the basis of individual genetic variations and may decrease the amount of time needed to identify the most beneficial drug and dosage for a patient, minimize exposure to ineffective treatments, reduce adverse drug reactions, and improve the economic efficiency of the health-care system. In view of the various perceived and real barriers and disincentives to investment in individualizing research by drug and device developers and reluctance of payers to cover the test, further guidance from the regulatory agency has been cited as an important next step in encouraging these developments.

The FDA has held open workshops to discuss critical issues in drug-test co-development, biomarker development, and clinical trial design and analysis. Concept papers and guidance are being developed. Various consortia set up to encourage data sharing have been obtaining results[9,10,24] and will need to continue in order to advance real personalized medicine (i.e., is this the correct drug and dose for this patient?).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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