BACKGROUND
ICH guidelines emphasise the need for a better understanding of the influence of ethnicity on drug response to minimise duplication of clinical studies, thereby expediting drug approval.
We have developed a Chinese data base for the ‘bottom-up’ prediction of differences in the population pharmacokinetics of drugs mainly metabolised by cytochromes P450 (CYPs) relative to Caucasian populations.
Such predictions should help to inform the need for duplication of in vivo PK studies in the two ethnic groups and the design of such studies.

METHODS
Demographic and physiological data for Chinese, along with information on CYP abundances and the frequencies of associated genetic polymorphisms in Chinese were collated from literature sources and incorporated within the Simcyp Population-based Simulator® (v10.0).
Default Simcyp parameter values for a virtual Caucasian population and for model compounds metabolised principally by specific CYPs were used.
The drugs and the main CYP involved in their metabolism were desipramine (CYP2D6), tolbutamide (CYP2C9), omeprazole (CYP2C19) and midazolam (CYP3A).
Observed plasma drug concentration – time profiles after oral administration were obtained from published in vivo studies in both Chinese and Caucasian subjects.
Virtual subjects generated within Simcyp were matched to the subjects used in the in vivo studies with respect to age, sex, dosage and, where possible, CYP phenotype frequency.
Predicted and observed plasma drug concentrations and weight normalised clearances were compared between the ethnic groups.

RESULTS
The following significant differences were identified between Chinese and Caucasian populations:
- CYP2C19 poor metaboliser (PM) frequency (Figure 1),
- CYP2D6 PM and intermediate metaboliser (IM) frequency (Figure 1),
- Hepatic CYP2C19 abundance (Figure 2A),
- Liver volume (Figure 2B).
Reported hepatic abundances per gram of liver of CYP2C9 and CYP3A4 are similar in Chinese and Caucasians. However, a lower liver weight propagates 30% lower net levels of these enzymes in Chinese.
No data on the hepatic abundance of CYP2D6 in Chinese were available. A mean value of 5 pmol/mg determined from Japanese livers was assumed (c.f. 8 pmol/mg for Caucasian livers).

CONCLUSIONS
The results of this study indicate the value of simulation based on a mechanistic PK/PD model in anticipating the likely extent of any differences in the kinetics of CYP substrates in Chinese and Caucasian populations arising from demographic, physiological and genetic differences.
Extension of this to predict the impact of such differences on the handling of drugs by transporters is indicated.

REFERENCES