

# WHAT POPULATION PK ANALYSIS CAN BE USED FOR IN DRUG DEVELOPMENT

The application of the “population approach” to pharmacokinetics, otherwise known as non-linear mixed effects modelling, is widely mentioned in ICH, FDA and CHMP guidelines. The approach is a powerful tool for obtaining pharmacokinetic (PK) information to support new drug development.

## POPULATION PK APPROACH

A population PK approach can be exploited throughout drug development using data from single or pooled across multiple studies in both healthy subjects and target patients. A major strength is that both sparse and rich data can be used and integrated with these type of models, with accurate estimation of the variability within and between individuals. The methodology may especially be applied to provide information about potential changes in the dose-exposure relationship for special populations (elderly, paediatrics, renal and hepatic impairment, etc) as an alternative to conducting specific studies. The usefulness of the population PK approach will, however, be highly dependent upon whether the inclusion/exclusion criteria are sufficiently flexible to allow a sufficient range of a given covariate of interest (e.g. age) to be studied. If insufficient patients are included over the range of the covariate, then specific studies may still be required.

The use of the population approach to evaluate drug PK in paediatric populations is the subject of dedicated guidelines from ICH, FDA and CHMP and is the preferred approach in this patient group. Specific care must be taken when planning the studies in which paediatric data will be obtained to ensure that the sparse sampling schedules that are commonly employed are strategically defined so that they will contain as much information about the PK of the drug in question as possible.

## IDENTIFYING POTENTIAL INFLUENCES OF BODY WEIGHT AND AGE ON PK

One of the most common current uses of population PK is to identify the potential influences of demographic and patient specific factors such as body weight, age, sex, race and disease on the PK of the drug under study. The potential influence of mild to moderate organ impairment is another common use. Again, it is important that sufficient patients are included and that PK sampling schedules are sufficiently informative. Phase III confirmatory studies often include PK data collection for this purpose. Confirming the absence of unsuspected drug-drug interactions may also be important information that can be included in the drug label, although attention must be paid as to when the potentially interacting drug was taken relative to the intake of the new drug under study in order for the results obtained to be considered valid.

## INTERACTIONS BETWEEN COVARIATES

One extremely powerful advantage of the population PK approach is to be able to provide information about interactions between covariates: for example, the possible change in dose-exposure for elderly women. Studies that look at the interaction between covariates (such as age and sex) are almost never performed, but the demand for this kind of information from regulatory authorities is increasing as they

seek to be able to put the side effect information into context for the whole potential demographic subgroup patient population. Another example involves the bridging of data between Japanese and global studies and whether potential differences in exposure can be explained by differences in body weight or if there exist additional ethnic differences warranting dose adjustments.

Once developed, population PK models can be used for simulation to illustrate the impact of covariates on the proposed and alternative dosage regimens on the PK of the new drug. The results from such simulations can also have an impact on eventual drug label information.

## INPUT FOR POPULATION PHARMACODYNAMIC MODELLING

Finally, population PK models may be used to provide exposure input for population pharmacodynamic (PD) modelling. Population PK/PD models, in which the full dose-exposure response relationship may be described simultaneously as a function of time, are becoming more and more important in drug development going forward, as industry, regulators, and payers seek to better understand the efficacy and safety of new drugs.

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