Mechanistic Deconvolution Using the ADAM Model: Part 2. Designing a New Once Daily Formulation for Metoprolol based on Mechanistic IVIVC and Studying the Population Variability in its Pharmacokinetics.

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PURPOSE

To demonstrate the application of the Physiologically based Advanced Dissolution, Absorption and Metabolism (ADAM)[1] model to design putative once-daily formulation for metoprolol and study population variability in its pharmacokinetics.

METHOD:

Designing New Formulation: A three-step process was followed: 1) a desired plasma metoprolol concentration profile lying within the reported therapeutic range (20–100 ng/mL)[2] for up to 24 h was defined based upon the known disposition characteristics of metoprolol (Fig. 1); 2) the *in vivo* dissolution profile required to achieve the desired plasma concentration profile was deconvoluted using the Simcyp ADAM model (Fig. 2); 3) this *in vivo* dissolution profile was converted to the desired *in vitro* dissolution profile based on the established and validated IVIVC (**AAPS AM 2012 Poster #: T2125**)[3] (Fig. 2).

Studying Population Variability: Inter-individual variability in the PK of the designed formulation after single dose and at steady state after multiple dose was studied by simulating 10 clinical trials with 10 healthy North European Caucasian volunteers (50% female) aged 20 to 50 years (Fig. 3). The Simcyp modelling platform allows users to define study populations (Caucasian, Chinese, Japanese, Obese, Diseased, etc.). Two types of data and corresponding variability were incorporated during simulations, namely: Physiological (population-dependent), and Drug-Specific (depends on characteristic of the drug and formulation)[3,4]. Metoprolol is mainly metabolised by the CYP2D6 enzyme which exhibits wide phenotypic variations. The retrograde calculator within Simcyp allows estimation from overall plasma clearance (CL) to intrinsic clearance (CL_{int}) by particular enzymes if the fraction metabolised by that enzyme (f_m) is known. This feature allowed us to study the PK of the formulation in subjects with various phenotypes of CYP2D6 (Extensive Metaboliser (EM); Poor Metaboliser (PM) and Ultra-rapid Metaboliser (UM)) (Fig. 4).
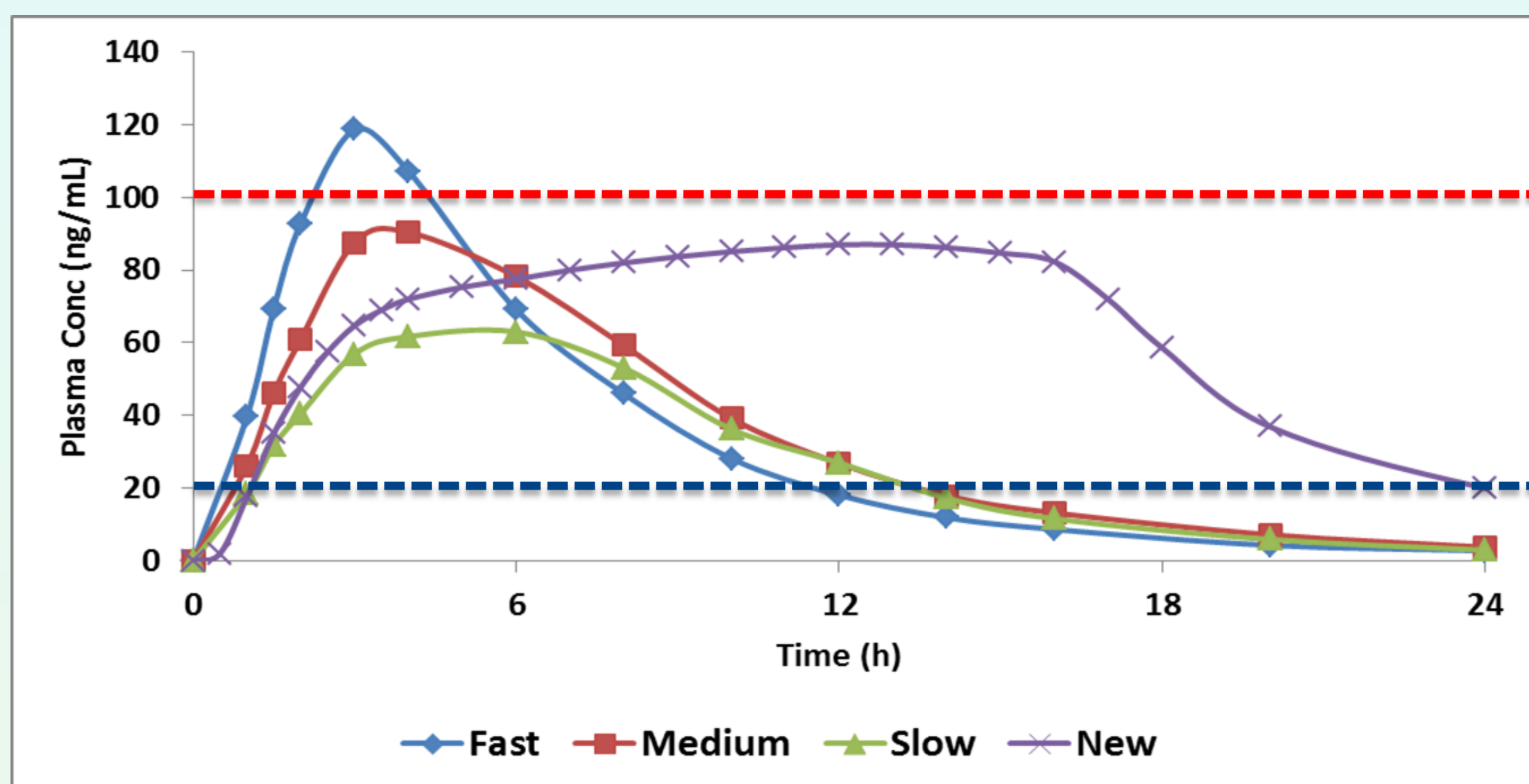

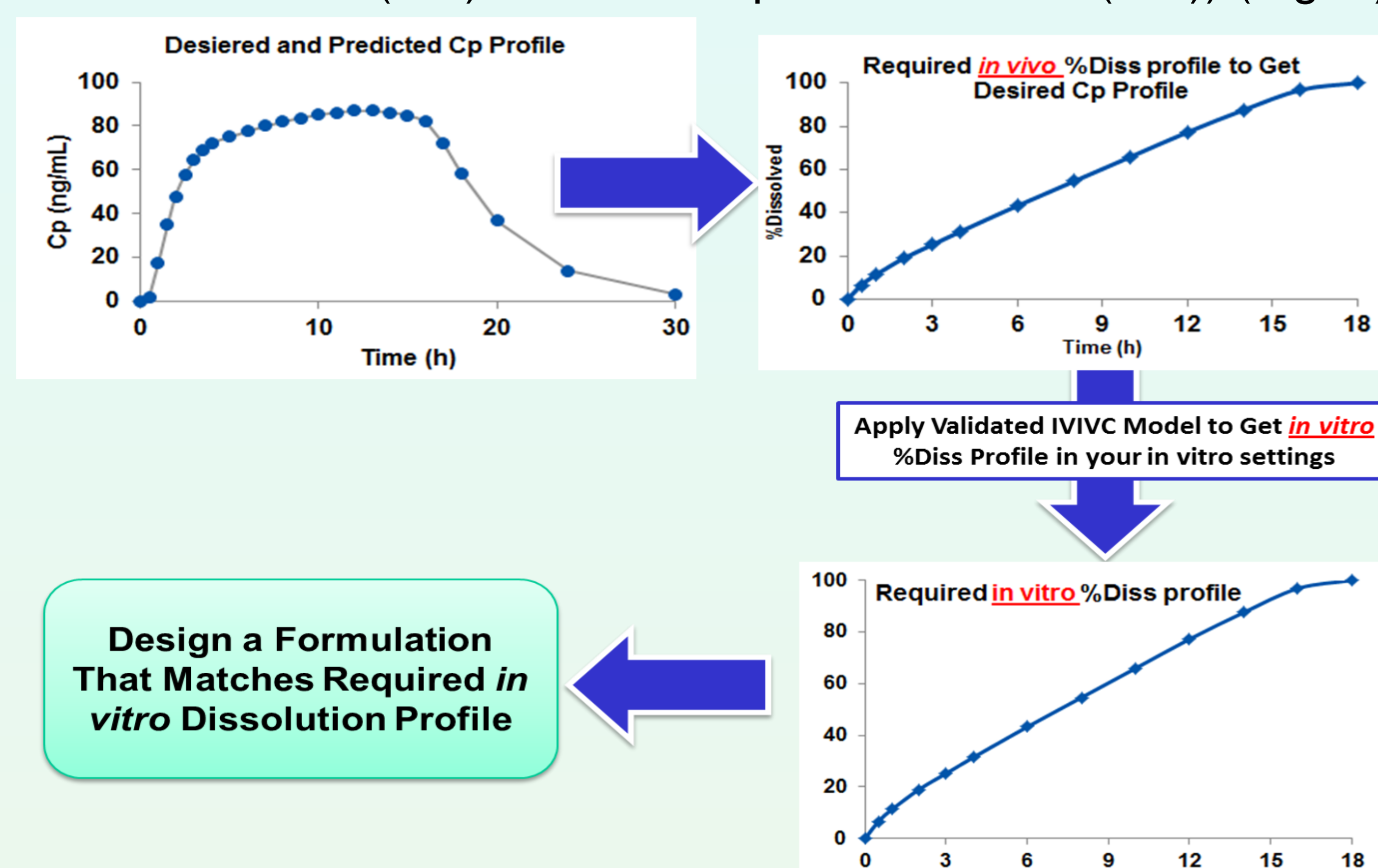Figure 1. Designing desired pharmacokinetic profile for new formulation

Figure 2. Obtaining required dissolution profile for desired pharmacokinetic profile

RESULTS:

Formulation was designed to have complete release between 16-18 hours coinciding with mean intestinal residence of an average north European Caucasian subject (Fig. 2). PBPK simulations could help to optimise clinical trials, identify covariates and deciding the dosage strengths to be studied for new formulation (Fig. 4).
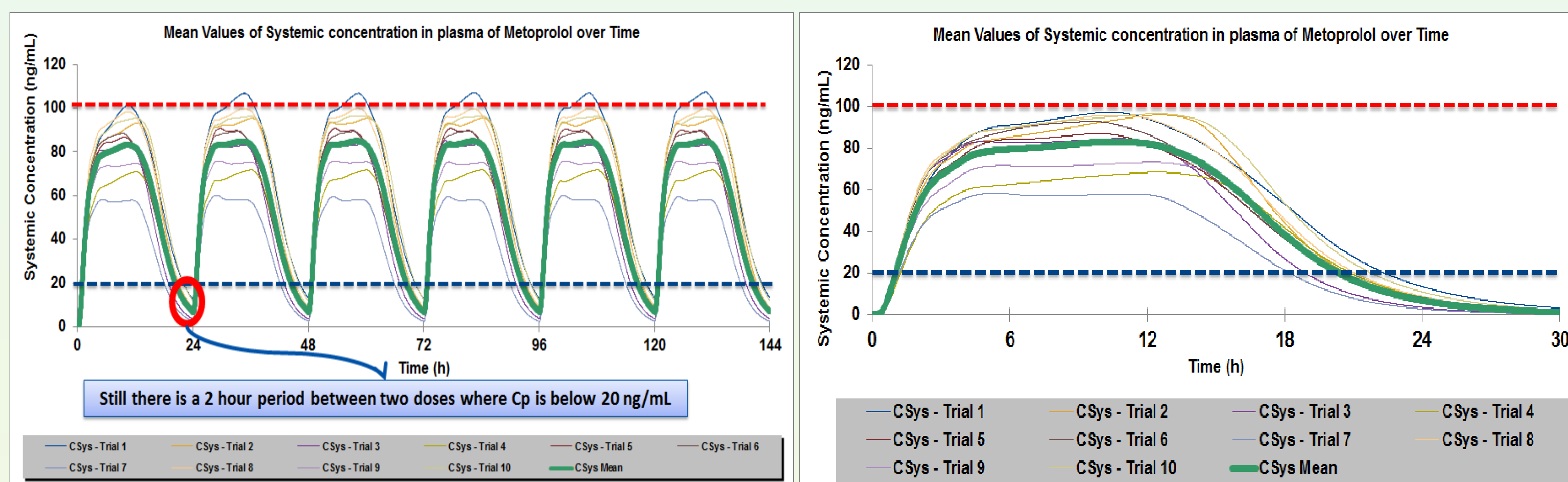

Figure 3. Simulating population variability after single and multiple dose of new formulation
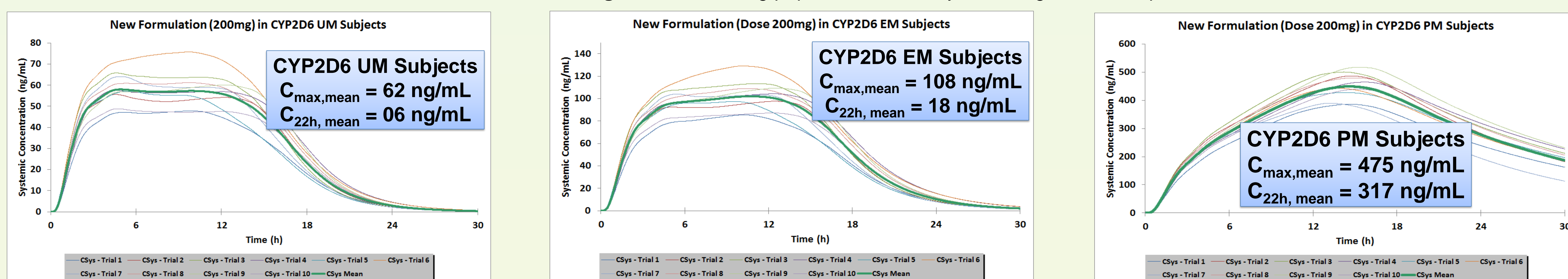
CYP2D6 UM Subjects
$C_{max,mean}$ = 62 ng/mL
$C_{22h, mean}$ = 06 ng/mL

CYP2D6 EM Subjects
$C_{max,mean}$ = 108 ng/mL
$C_{22h, mean}$ = 18 ng/mL

CYP2D6 PM Subjects
$C_{max,mean}$ = 475 ng/mL
$C_{22h, mean}$ = 317 ng/mL

Figure 4. Simulating population variability in subjects with different phenotypes (PM, EM, UM) of CYP2D6

CONCLUSION:

Mechanistic deconvolution approaches, exemplified by the ADAM model, are potentially very useful tools in designing and evaluating performance and safety of new formulations. Further validation using a range of drugs with different biopharmaceutical properties is needed to improve confidence in and increase the awareness and acceptance of such mechanistic IVIVC approaches in formulation design and optimisation.

REFERENCES:

1. Jamei *et al.* (2009) AAPS J; **2.** Aqil *et al.* (2007) Clin Drug Investi.; **3.** Patel *et al.* (2012) AAPS AM 4. Jamei *et al.* (2009) DMPK; **4.** Rostami-Hodjegan (2012) CPT