THE COCKTAIL APPROACH AND ITS UTILITY IN DRUG–DRUG INTERACTION ASSESSMENTS FOR THERAPEUTIC PROTEINS

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7.1 ASSESSMENT OF ENZYME ACTIVITIES USING THE COCKTAIL APPROACH

The cocktail approach is used to assess the effect of drugs on the activities of the main cytochrome P450 (CYP) enyzmes *in vivo*. As for all other drugs, any effect of therapeutic proteins on the metabolism of other (victim) drugs needs to be tested and quantified. The main mechanisms of interaction for small molecules on CYPs are enzyme inhibition by direct interaction with the enzyme, increased synthesis of enzymes via aryl hydrocarbon (Ah)- or retinoid X receptor (RXR) related processes, or decreased turnover of the enzyme (in the case of the cytochrome P450 enzyme CYP2E1). These mechanisms of interaction are related to the structural similarity of victim substrates and other small molecule drugs. Appropriate *in vitro* tests have been established for enzyme inhibition and, with limitations in quantification of the effect, also for the described mechanisms of enzyme induction. In contrast, therapeutic proteins would rarely have a direct action on the enzyme or would trigger classical enzyme induction, which developed as specific defense mechanisms to protect an organism against exposure to toxic nutritional components. Thus *in vitro* or animal studies with therapeutic proteins have limited power to predict clinical interactions because the molecular mechanisms are only partially understood and/or often cannot be mimicked in nonclinical test systems.[1] Because not all potential combinations of a therapeutic protein with other drugs can be tested in a clinical study, the effect of such drugs on drug metabolizing enzymes, mainly

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