



The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

London, 17 December, 1997
CPMP/EWP/560/95

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
(CPMP)**

**NOTE FOR GUIDANCE ON
THE INVESTIGATION OF DRUG INTERACTIONS**

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	June/October 1996 February 1997
TRANSMISSION TO THE CPMP	March 1997
TRANSMISSION TO INTERESTED PARTIES	March 1997
DEADLINE FOR COMMENTS	September 1997
RE-SUBMISSION TO THE EWP	December 1997
APPROVAL BY THE CPMP	December 1997
DATE FOR COMING INTO OPERATION	June 1998

THE INVESTIGATION OF DRUG INTERACTIONS

This note for guidance should be read in conjunction with the following:

- The CPMP guideline for Good Clinical Practice.
- The CPMP guideline on Investigation of Bioavailability and Bioequivalence.
- The CPMP guideline on Pharmacokinetic Studies in Man.
- The CPMP guideline on Analytical Validation.
- The CPMP guideline on Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products.
- The CPMP guideline on Investigation of chiral active substances.
- The CPMP safety guideline on Pharmacokinetics and Metabolic Studies in the Safety Evaluation of New Drugs in Animals.
- The CPMP safety guideline on Repeated Dose Toxicity.
- The CPMP safety guideline on Single Dose Toxicity.
- The CPMP guideline on clinical investigation of medicinal products in children.
- The CPMP guideline on fixed combination products.

1. INTRODUCTION

As a consequence of the scientific development within the areas of pharmacokinetics (particularly drug metabolism) and pharmacodynamics, the focus of interaction studies has changed from ad hoc observational studies to rationally designed studies. Depending on structural and physio-chemical characteristics and human *in vitro* data, selective *in vivo* studies may be performed. Based on results from such studies, the risk of clinically relevant interactions may be predicted. As a consequence, the information provided to the prescriber has also become more extensive and scientific.

The objectives of this Note for Guidance are to:

- Outline requirements for interaction studies on new chemical entities on the basis of their physico-chemical, pharmacokinetic and pharmacodynamic properties.
- Propose a structure for the presentation of the information obtained in the SPC.

In addition, the guideline aims to define the *in vivo* studies needed thereby reducing the number of preclinical and clinical studies.

In this document, an 'interaction' is defined as an alteration either in the pharmacodynamics and/or the pharmacokinetics of a drug, caused by concomitant drug treatment, dietary factors or social habits such as tobacco or alcohol. Other factors that may interact to alter drug disposition such as age, gender, physical activity, ethnic origin and time of administration will not be discussed in this guideline.

It is accepted, that for many compounds which have a wide therapeutic margin, pharmacokinetic drug interactions may have little clinical significance.

2. CLINICALLY RELEVANT INTERACTIONS

It is important in the drug development phase to differentiate between detectable interactions and clinically relevant interactions.

An interaction is 'clinically relevant':

- When the therapeutic activity and/or toxicity of a drug is changed to such an extent that a dosage adjustment of the medication or medical intervention may be required.
- When concomitant use of the two interacting drugs could occur when both are used as therapeutically recommended.

To appreciate fully the potential of a new drug for clinically relevant interactions, the following aspects should be taken into account during the drug development program:

- Extensive characterisation of the physico-chemical properties of the drug.
- Early characterisation of the full pharmacodynamic profile and pharmacokinetic properties of the drug and the factors that may alter these.
- *In vitro* data should mainly be used qualitatively. If no interaction is detected in an appropriately performed *in vitro* study, then there is no need to perform an *in vivo* study. If an interaction is indicated from *in vitro* data, applicants should design and perform relevant *in vivo* studies.
- If appropriately performed *in vitro* studies indicate the lack of an interaction, *and* if a claim of "No clinically relevant interaction with Drug X" is desired in the interaction section of the SPC, then a confirmatory *in vivo* studies will be required.
- Preferably, both pharmacokinetic and when relevant pharmacodynamic variables should be studied in the *in vivo* interaction studies. The clinical relevance of the results for the *in vivo* studies should be discussed in light of the dose/concentration-effect (therapeutic as well as toxic) relationships for the drug, if these are known.
- The studies should focus on both the effect of the new drug on already approved drugs and the effect of already approved drugs on the new drug.

3. PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic actions may include both therapeutic and adverse effects of drugs. Extensive pharmacological and toxicological knowledge about the drug is crucial for the performance of a meaningful pharmacodynamic interaction study.

Pharmacodynamic interactions may be caused by a large variety of mechanisms. It is therefore impossible to give detailed guidance for pharmacodynamic studies, where the design must be determined on a case-by-case basis. When similar mechanisms and/or effects are found in animals and in humans, animal studies can be used to characterise a potential interaction. In general, animal, *in vitro* and clinical studies together will better describe the pharmacodynamic interaction profile of a drug.

The need for pharmacodynamic interactions studies should be determined on a case by case basis, taking into account the following points:

- When drugs likely to be co-administered have similar mechanisms of action or potentially interaction mechanisms of action.
- When drugs likely to be co-administered have similar or opposing pharmacodynamic effects.

When designing pharmacodynamic studies, it must be remembered that:

- An interaction may be due to direct competition at a particular site of action or could be indirect involving altered physiological mechanisms or sensitivity of the systems affected.
- Both the therapeutic and the toxic effects can be altered by pharmacodynamic interactions.
- Pharmacodynamic interactions may involve interaction between therapeutic activity of one compound with toxic effect of another compound.
- Therapeutic activity and toxic effect might be affected in different directions resulting in a modified balance between positive and negative properties.

4. PHARMACOKINETIC INTERACTIONS

4.1 Absorption

This guideline focuses on absorption interactions in the gastro-intestinal tract. Absorption interactions may, of course, also occur at other absorption sites, for example, following dermal or nasal administration. It should be noted that a drug given by another route of administration such as the intravenous route could have an impact on the gastro-intestinal absorption, by a pharmacodynamic effect on, for example, gastro-intestinal secretion or motility.

In the case of an interaction, rate of absorption, fraction absorbed and first-pass metabolism may be influenced. Normally, a change in the bioavailability is of particular clinical importance.

P-glycoprotein is gaining increasing recognition of its involvement in the process of drug absorption. The regulatory implications of the actions of P-glycoprotein and interactions with its function are, as yet, undefined. P-glycoprotein may contribute to a low drug absorption by decreasing the effective membrane permeability of the drug. It has been reported that many substrates for P-glycoproteins are also substrates for CYP3A4. Consequently many drugs might first be effluxed by P-glycoproteins and then absorbed again, thus undergoing a local recycling process that might result in an increased presystemic metabolism due to a decreased presentation rate for the CYP3A4 inside the enterocyte. Drug interactions at the intestinal epithelium might therefore affect bioavailability by changes in absorption and/or first pass metabolism. The presence of this protein in the gut should be borne in mind when designing and interpreting interaction studies.

In vitro studies may be helpful in investigating transport mechanisms or the potential of a drug for complex binding/chelation. Since current *in vitro* absorption studies have been shown to have limited value for *in vivo* absorption, potential interactions should be confirmed by well designed *in vivo* studies.

When deciding on what absorption studies are needed, the following should be considered:

- The effect of food should always be studied with new drugs intended for oral administration or with new modified release dosage forms. For a new drug it is important to determine if the food is influencing the drug substance and/or the dosage form.
- Drug-drug absorption interaction studies should be performed when co-medication of the two drugs could influence the absorption process of either drug. The decision to perform drug-drug interactions studies should be based on a combined knowledge of the two drugs' properties. Those are:
 - ♦ Factors known to influence drug absorption including the effect of food.
 - ♦ Physico-chemical properties of the drug substance and formulation (pH dependency, solubility, dissolution, ability for complex formation/chelation/adsorption).
 - ♦ Pharmacokinetic properties (in particular absorption mechanisms, bioavailability, extent absorbed and first pass metabolism, biliary excretion, enterohepatic recycling).
 - ♦ Pharmacodynamic properties (in particular effects on the gastrointestinal physiology such as gastric emptying and motility, gastric pH, bile secretion, splanchnic blood flow, gastrointestinal flora).
 - ♦ Toxic effects such as damage of gastrointestinal membranes.

When designing absorption interaction studies, it must be remembered that:

- Food-related interactions should preferably be investigated early in drug development process so that the information obtained may be considered in the design of the Phase II and III studies.
- Food or other drugs may influence drug absorption for several hours. If a significant interaction is demonstrated, the dosage recommendations (i.e. timing of dose in relation to the interacting agent) should be adequately validated in the clinical situation.
- Dosage forms sensitive to food effects should be avoided if possible.
- Factors/mechanisms causing the interaction should be identified wherever possible.

4.2 Distribution

Displacement of drug from plasma proteins is the most common explanation for altered distribution in drug interactions. However, few displacement interactions result in clinically relevant changes.

Displacement interaction studies should be performed when the investigated drug:

- Has non-linear protein binding.
- The volume of distribution is small.
- Has a narrow therapeutic index *and*
- Is highly bound (>95%) to proteins in human plasma at therapeutic concentrations *and*
- Occupies most of the binding sites (e.g. plasma therapeutic concentrations at the highest recommended dose exceed the plasma binding capacity).

In addition to above mentioned conditions, a displacement study should be performed:

- After a single dose or at initiation of therapy (starting or loading dose) when the volume of distribution of the investigated drug is small ($< 10L/70\text{ kg}$).
- When the investigated drug is administered intravenously *and* possesses a high metabolic extraction ratio.

When designing displacement interaction studies, it must be remembered that:

- Displacement studies should be preferably performed *in vivo*, since the metabolites of the drug may also be involved in such interactions. If such studies are performed *in vitro*, then the possible contribution of metabolites to an interaction should be considered.
- Changes in unbound plasma concentration may not occur in parallel with the total plasma concentration.

4.3 Elimination

Many known clinically relevant interactions are due to changes in the elimination of drugs. Therefore, information of immediate interest early in the development of a new drug is the relative clearance by metabolic and non-metabolic routes.

4.3.1 Metabolism

The primary metabolic pathway(s), the primary site of metabolism for the drug, and the proportion of the total clearance that each primary metabolic pathway constitutes should be determined at an early stage. Furthermore, the enzyme(s) responsible for the metabolism, potential effects of their inhibition or induction, and possible polymorphism in the metabolism should be investigated. The major drug metabolising CYP450 enzymes are listed in Table 1.

Depending on the properties of the drug, and the route of administration, different effects on the unbound plasma concentration could be expected when the intrinsic clearance or the liver blood flow are changed. Furthermore, it has to be taken into account that the outcome of metabolic drug interactions could be more serious in cases of steep dose/concentration-response curves.

As a general guidance, *in vitro* and/or *in vivo* metabolic interaction studies should be performed for metabolic pathways responsible for 30% or more of the total clearance. However, if toxic/active metabolites are formed minor metabolic pathways may also need to be studied.

In vitro data, that take into account potential metabolite influences, may be used to demonstrate lack of interaction. *In vitro* studies showing a possible interaction should be followed by adequate *in vivo* studies.

4.3.1.1 Change of intrinsic clearance

An inhibition or induction of the metabolism resulting in a change of the intrinsic clearance could cause a change of the unbound plasma concentration at steady state for "low extraction drugs" administered orally or intravenously, and for "high extraction drugs" administered orally. On the other hand, there is no change of the unbound plasma concentration at steady state for "high extraction drugs" administered intravenously.

4.3.1.1.1 Metabolic induction

Clinically relevant induction occurs during multiple dosing of the inducing drug and is a dose and time dependent phenomenon.

Points to consider regarding metabolic induction:

- Decide if the relevant enzyme(s), is (are) inducible or not.
- Time is required for the onset and offset of induction.
- When metabolites are pharmacologically active, it should be remembered that the introduction of an inducer may result in an increase in the concentration of the metabolites, possibly resulting in an increased effect.
- The clinical effects of induction might be more serious when the inducer is abruptly withdrawn.
- Many dietary and social habits such as eating charcoal grilled meat or smoking may induce drug metabolism.

4.3.1.1.2 Metabolic inhibition

Inhibition is also a dose dependent phenomenon but in contrast to induction, clinically relevant inhibition can occur quickly. In inhibition processes, both the oxidative, the hydrolytic and conjugation pathways may be involved, inhibition of the oxidative enzymes being clinically the most common.

Points to consider regarding metabolic inhibition:

- Most inhibition is competitive and disappears rather rapidly as soon as the inhibitor is eliminated or decreases after the dose is reduced.
- In contrast to induction, inhibition is often enzyme specific.
- When metabolites are pharmacologically active, it should be remembered that the introduction of an inhibitor may result in a decrease in the concentration of the active metabolites, thereby possibly reducing their effect.
- Some dietary constituents are known inhibitors of specific drug metabolising enzymes, e.g. grapefruit juice (CYP3A4).

4.3.1.2 Change of blood flow

In general, a change of the blood flow through the liver causes no change of the unbound plasma concentration at steady state for "low extraction drugs" administered orally or intravenously, and for "high extraction drugs" administered orally. On the other hand, a change of the unbound plasma concentration at steady state for "high extraction drugs" can be expected if administered intravenously.

4.3.1.3 Metabolic interaction studies

When designing metabolic interaction studies, it must be remembered that:

- The relevant enzyme kinetic parameters should be determined. K_m allows prediction of the potential of the drug as a competitive inhibitor of the metabolism of other drugs by a particular enzyme, and is also used to define the potential of other drugs to inhibit the

metabolism of the new drug. The likelihood for a potential *in vivo* interaction depends on the relative K_i and K_m of the two drugs involved, and their relative *in vivo* concentrations.

- The potential of the new drug to inhibit specific drug metabolising enzymes including important enzymes for which the drug is not a substrate should be defined. The K_i for potent interactions should be determined to allow *in vivo* predictions.
- Interactions predicted from *in vitro* data should be investigated *in vivo*. *In vitro* predicted drug interactions may indicate the need for contraindications or towards caution in use without confirmatory *in vivo* studies. If dosage alterations are required, these should be confirmed *in vivo*.

4.3.2 Renal excretion

Interactions at the level of renal excretion have been reported for many drugs where renal excretion is the dominant route of elimination. The role of renal elimination in the excretion of active metabolites is just as important in the context of such interactions.

For drugs where the renal route is an important route of elimination, interactions could occur via changes in protein binding (glomerular filtration rate), urinary pH and/or urinary flow rate (passive reabsorption) and by competition of active secretion in the renal tubule.

Renal excretion interaction studies should be performed:

- When the renal elimination is an important route of elimination of either parent and/or pharmacologically active or toxic metabolites *and*
- When the drug/active or toxic metabolite is excreted by active secretion or there is an indication of significant reabsorption.
- Consideration should be given to performing renal interaction studies when the drug is not predominantly excreted in the urine but has a low therapeutic index.

When designing renal excretion interaction studies, it must be remembered that:

- The alteration of pH may be clinically significant if the pK_a value of the drug is in the range of about 7.5 - 10.5 for bases, and 3.0 - 7.5 for acids.
- Of the two secretion pathways, the one for acids appears clinically to be the more prominent pathway for interactions.
- The potential for interactions involving active renal secretion could be studied using *in vitro* methods prior to *in vivo* studies.

Examples of drugs actively secreted into the renal tubule are given in Table 2.

4.3.3 Hepatic/biliary excretion

For drugs where the biliary route is an important route of elimination, and for which a saturation of the excretory capacity of the liver is possible, interactions caused by competition for hepatic excretion should be considered. The possibility for drugs to interfere with enterohepatic circulation should also be considered. Interactions at the level of hepatic excretion have been reported for a few drugs (e.g. rifampicin).

5. POINTS TO CONSIDER WHEN DESIGNING AND ASSESSING INTERACTION STUDIES

One advantage of performing drug interaction studies early in the drug development process is that knowledge of causes for variability, such as food interactions, can be taken into consideration in the design of Phase II and Phase III studies. Thus, extensive investigation of potential interactions at an early stage of drug development is encouraged.

5.1 Mechanism based *in vivo* studies

When studying the effects of inhibition or induction on the pharmacokinetics or pharmacodynamics of a new drug, the following should be considered:

- Most of the time *in vivo* pharmacokinetic interaction studies could be performed in healthy volunteers, while *in vivo* pharmacodynamic interaction studies may be performed in patients or healthy volunteers depending on the situation and the pharmacodynamic effect measured. Disease-related interactions should always be considered.
- Subjects participating in metabolic *in vivo* interaction studies should be appropriately genotyped and/or phenotyped if any of the active enzymes mediating the metabolism are polymorphically distributed in the population. In some cases, clinically relevant interactions may only occur in a subset of the total population, for instance, slow-metabolisers, when an alternative route of metabolism is inhibited.

5.1.1 Experimental design

When designing interaction studies it must be remembered that:

- What is the question - The effect of inhibition/induction, or, the effect of a specific drug? If it is the effect of inhibition/induction, then the pharmacokinetic parameters of the inducer or the inhibitor should be carefully considered and steady state conditions be achieved whenever possible. Approved therapeutic dose regimen for the selected inhibitor or inducer may not be optimal to obtain a full inhibitory or inducing effect. The number of daily doses may have to be increased to ensure inhibition/induction over 24 hours. Similarly, the duration of pre-treatment with an inducer should be sufficient to maximise the influence on the metabolic system. If the question concerns the effect of a specific drug, then that drug's approved therapeutic regimen should be used.
- Sufficient time must be allowed to reach a pharmacokinetic and pharmacodynamic steady-state. To provide adequate dosage recommendations to the prescriber, the off-set of induction may be important to study as well.
- In order to reduce variability, a cross-over design is usually appropriate. Other designs may be chosen in specific situations, but should be justified in the study protocol.
- In studies involving simple induction or inhibition, it may be adequate to investigate the effect of one drug on the pharmacokinetics of the drug in question. However, when the two drugs are substrates of the same enzyme, it is important to investigate the pharmacokinetics of both the drugs administered singly and in combination to the same cohort in order to evaluate the effect of each drug on the other. The sequence of administration of both drugs also needs to be considered.
- In most *in vivo* pharmacokinetic studies it seems reasonable to focus on the exposure of the drug, AUC and the two variables determining this, i.e. extent of absorption, F, and clearance (CL). Other parameters may also be of importance such as C_{max} and t_{1/2}, especially if the safety issue is dependent on the pharmacological action of the product.

- The number of subjects should always be justified.
- The precision of the estimate of the magnitude of any potential interaction must be considered.

5.1.2 Statistical analysis

In the statistical analysis it should be remembered that:

- The statistical analyses of the treatment effects of interest should in general be carried out by means of analysis of variance and should include the calculation of confidence intervals for the estimates of the size of the effects.
- To demonstrate the lack of a relevant interaction, the inclusion of the 90% confidence interval for the ratio/difference of the means within some prespecified acceptance range is generally suitable. If appropriate, the pharmacokinetic parameters to be compared should be logarithmically transformed before analysis. When considering potential therapeutic consequences of an interaction (dosage reductions or increases), the acceptance range to conclude lack of interaction may be wider (or narrower) than the interval of 80% to 125% commonly used in establishing bioequivalence.
- If this fails, the point estimate together with the confidence interval should form the basis for any potential recommendations of dose modifications.

These methods for comparison of means are appropriate in most situations. However, the consequence of an interaction might be increased variability, so, for drugs with a narrow therapeutic index, designs and methods that focus on the analysis of variability might be necessary. The statistical analysis of variability needs special attention. In certain situations the percentage of patients who show/have a prespecified event may be of more interest and then the analysis should focus on this.

5.1.3 Interpretation of mechanism based studies

It seems reasonable that *in vivo* studies with strong inducers/inhibitors may be used to extrapolate qualitatively to other inducers/inhibitors of the same enzyme. Similarly, effects of the new drug on substrates should be qualitatively transferable to other substrates for the same enzyme.

5.2 Population studies

It is often valuable to include a population approach in Phase II/III clinical trials to screen for pharmacokinetic drug interactions. Valuable additional information is then obtained from studies that are performed for other reasons. It is, however, important to remember that in the context of the population approach, these studies may not be randomised and can therefore be subject to the usual bias of observational studies. The outcome should mainly be used as hypothesis-generating and the best use of this approach can probably be made to highlight unsuspected interactions and possibly to confirm absence of suspected interactions. The successful use of such an approach is highly dependent upon the protocol inclusion criteria so that:

- Sufficient numbers of patients taking the potentially interacting drug exist (to avoid falsely not finding an interaction).
- Information should be available as to when the interacting drug was taken, *and* should be within a reasonable time frame with respect to when the test drug was administered.

In order to avoid drawing incorrect conclusions, in particular false negative conclusions, certain aspects of analysis need special attention, because the statistical models and computational procedures used to analyse population pharmacokinetic studies can be particularly complex. It is important to ensure that the particular models chosen and procedures used are reliable, and are appropriate for the statistical distribution of the data. In addition, the influence of potential confounding factors, such as age or other demographic or pathophysiological characteristics, on the results and conclusions should be checked, bearing in mind the potential lack of randomisation and the possibility for bias.

A confidence interval associated with the estimate of the interaction should be presented. This is particularly important if no significant interaction is detected in order to permit an assessment of the degree of interaction potentially excluded.

6. INFORMATION IN THE SPC

The information in the SPC should follow the general guideline outlined in the Notice to Applicants. However, the increased knowledge of factors influencing potential interactions and the possibility to study these factors in a selective mechanistic way also influences the way in which such information is provided to the prescriber. Information based solely on mechanisms is probably insufficient and the information should be clarified with examples. Relevant information should be included under the headings as outlined below. As pointed out below, serious clinical interactions should also be described either under "4.3 Contraindications" or "4.4 Special warnings and precautions for use" in the SPC. It should also be noted that lack of knowledge regarding drug interactions is not only an issue for the SPC, but could for a given drug, influence the risk/benefit assessment in the final opinion.

6.1 Clinical particulars

Examples of SPC-texts related to drug interactions are given below:

4.3 Contraindications

Drug X prolongs the QT interval and is contraindicated in patients treated with.....

4.4 Special Warnings and Precautions for Use

Drug X may prolong the QT interval and should be used with caution in patients concomitantly treated with

4.5 Interactions

Results from performed *in vivo* studies in humans should be described under this heading together with relevant potential interactions predicted from *in vitro* studies but not studied *in vivo*. It is important to clearly differentiate between effects of other drugs on the investigated drug, and effects of the new drug on other drugs. *In vivo* results showing lack of interaction could also be included when this information is valuable. The potential for renal interactions with other drugs has to be stated if renal elimination is an important part of total elimination.

The information could be worded as follows:

Drug X is a potent inhibitor of CYP3A4 and has been shown to increase the levels of triazolam. Hence, caution is advised when X is given together with other substrates for CYP3A4 such as The pharmacokinetics of X were not influenced by the CYP3A4 inhibitor ketoconazole.

Drug X has been shown to induce serotonergic syndrome in combination with MAO-inhibitors. Treatment with Y should not begin until two weeks after the cessation of treatment with MAO-inhibitors.

As mentioned above, the text should also discuss potential interactions which have not been addressed by the applicant. If relevant *in vivo* studies are not performed, the following text provides an example based on the results from performed *in vitro* studies:

Although interaction studies have not been performed, due to the potential enzyme induction, drug X should not be combined with drugs which are metabolised by CYP1A2 and which possess a narrow therapeutic index, such as...

or

Although interaction studies have not been performed, since this drug is metabolised by CYP3A4, it is expected that ketoconazole, itraconazole, clotrimazole, ritonavir..... inhibit its metabolism. On the other hand, inducers of this enzyme such as rifampicin, phenytoinmay reduce the levels of the drug. Since the magnitude of an inducing or inhibiting effect is unknown, such drug combinations should be avoided.

or

The haemodynamic properties of digoxin, noradrenaline and adrenaline would be expected to be potentiated in combination with drug Y. Hence, caution is advised if these drugs are given concomitantly.

6.2 Pharmacology

Relevant pharmacokinetic, metabolic and pharmacodynamic properties of the drug should be summarised under 5, e.g.

5.1 Pharmacodynamics

Drug X is an inhibitor of the reuptake of serotonin and noradrenaline.

5.2 Pharmacokinetics

Drug X is mainly metabolised by CYP3A4 and has demonstrated a capacity to induce this enzyme and CYP1A2, in vitro.

7. APPENDIX

7.1 Table 1: The major drug metabolising CYP450 enzymes, examples of substrates, inhibitors, inducers and markers.

P450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS	MARKERS
CYP1A2	Acetaminophen Aromatic amines Caffeine Phenacetin Theophylline	Fluvoxamine Furafylline	Charcoal-grilled beef Cigarette smoke Cruciferous vegetables	Caffeine
CYP2A6	Coumarin Butadien Nicotine	Diethyldithiocarbamate 8-methoxypsoralen Tranlycypromine	Barbiturates	Coumarin
CYP2C9	NSAID drugs Phenytoin Tolbutamide S-Warfarin	Sulfaphenazole Sulfinpyrazone	Rifampin Barbiturates	S-Warfarin Tolbutamide
CYP2C19	Citalopram Diazepam Hexobarbital Imipramine Omeprazole Proguanil Propranolol	Tranlycypromine	Rifampin Barbiturates	Mefenytol Omeprazole
CYP2D6	Several anti-depressants Neuroleptics Beta-blockers Antiarrhythmics Codeine Dextromethorphan Etylmorphine Nicotine	Ajmalicine Chinidin Fluoxetine Paroxetine Quinidine Ritonavir	None known	Debrisoquine Dextromethorphan
CYP2E1	Acetaminophen Alcohols Caffeine Chlorzoxazone Dapsone Enflurane Theophylline	Diethyldithio-carbamate Dimethyl sulfoxide Disulfiram	Ethanol Isoniazid	Caffeine Chlorzoxazone
CYP3A4	Acetaminophen Carbamazepine Cyclosporin Digitoxin Diazepam Erythromycin Felodipine Fluoxetine Nifedipine Quinidine Saquinavir Steroids (e.g. cortisol) Terfenadine Triazolam Verapamil Warfarin	Clotrimazole Ketoconazole Ritonavir Troleandomycin	Dexamethasone Phenytoin Rifampin Troleandomycin	Dapsone Erythromycin Ketoconazole Lidocaine

7.2 Table 2: Examples of drugs actively secreted into the renal tubule.

ORGANIC ACIDS	ORGANIC BASES
acetazolamide some cephalosporins chlorpropamide hippuric acid indomethacin loop diuretics methotrexate oxyphenbutazone penicillins phenylbutazone probenecid salicylic acid sulphonamides sulphonic acids thiazide diuretics	amantadine amiloride cimetidine dopamine ethambutol meperidine metformin N-methylnicotinamide morphine procainamide d-pseudo ephedrine quinacrine triamterene