

Transporters in drug development: advancing on the Critical Path

A new report from an international consortium provides comprehensive scientific recommendations for studies of transporter-related drug interactions in drug development.

In March 2004, the US FDA published a report¹ entitled: “*Innovation or Stagnation: Challenges and Opportunities on the Critical Path to New Medical Products*”. This paper focused on the concern that the timely translation of advances in biomedical research into more effective, affordable and safe innovative medical products was being impeded because drug development was becoming increasingly challenging, inefficient and costly. Recognizing that regulators have a key role to play in addressing this problem, the FDA launched the Critical Path Initiative to identify and prioritize the most pressing drug development issues and the greatest opportunities to address them, emphasizing the importance of collaboration among stakeholders.

In this issue, the International Transporter Consortium (ITC) — comprising experts in industry, academic groups and the FDA from the United States, Europe and Japan (see page 215) — presents a report² on membrane transporters in drug development that exemplifies the aims of the Critical Path Initiative. The report, which is based on discussions before, during and after a 2008 workshop supported by the FDA Critical Path Initiative and the Drug Information Association, has three goals. The first is to provide an overview of key transporters that are involved in drug absorption and disposition. The second is to provide examples of various technologies in studies of transporter-related drug–drug interactions, including computational methods that have been used to construct models for predicting such interactions. The third is to provide criteria for the design and conduct of clinical studies of transporter-related drug–drug interactions. These include decision trees to assist drug development scientists and regulatory personnel in determining when to conduct clinical studies to investigate transporter-related drug–drug interactions.

Transporters and drug safety

Drug–drug interactions are particularly important in the growing ageing populations in many countries, given the number of different drugs older people may be taking. For example, a recent survey indicated that more than 30% of the elderly population in the United States takes at least five prescription drugs at any given time³. Drug–drug

interactions can result in reduced efficacy or increased toxicity. Indeed, several drugs that have been withdrawn from the US market for safety reasons — such as terfenadine, astemizole and cisapride — demonstrated major drug–drug interactions.

Many of these drugs are metabolized by cytochrome P450 3A4 (CYP3A4), which has been estimated to be involved in the metabolism of ~50% of prescription drugs and is therefore a common cause of drug–drug interactions. Recent data suggest that transporters may also contribute to drug safety issues. For example, another withdrawn drug, mibefradil, which in combination with simvastatin caused several cases of rhabdomyolysis⁴, is an inhibitor of transporters such as P-glycoprotein, as well as of CYP3A4. It is possible that transporter-mediated drug–drug interactions may have played a part in this serious adverse drug reaction.

Further evidence of the important role of transporters in drug safety was provided by a genome-wide association study showing that particular polymorphisms in the liver transporter protein organic anion transporting polypeptide 1B1 (OATP1B1) increase the risk for statin-induced myopathy⁵. Given this, the FDA has also recently revised the drug label for atorvastatin to include information that atorvastatin and its metabolites are substrates of OATP1B1. The label also states that the daily dose should not exceed 10 mg when given with cyclosporine, which is a nonspecific inhibitor of transporters including P-glycoprotein and OATP1B1.

In addition, recent new drug applications (NDAs) have included information on OATP1B1, which have been incorporated in the drug labels of approved new molecular entities (NMEs). For example, eltrombopag, a thrombopoietin receptor agonist, was recently approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy. The label for eltrombopag, which is an inhibitor of OATP1B1, notes the importance of monitoring patients for potential overexposure to other drugs that are substrates of OATP1B1. It is also important to highlight when a certain drug interaction is not present or expected.

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As the field of membrane transporter research is evolving rapidly, transporter-specific information in NDA submissions may not have been included in the pre-marketing approval decision, especially for drugs in therapeutic areas for which there are major unmet medical needs, such as oncology. Therefore, the FDA has recently asked for post-marketing studies of potential transporter-mediated drug–drug interactions. A review of recent post-marketing commitment (PMC) and post-marketing requirement (PMR) reports⁶ indicated that more than a quarter of the clinical pharmacology PMC and PMR reports were related to drug–drug interactions. Of these, many of the more recent requests were related to evaluation of potential transporter-based drug–drug interactions. Results from these studies, when completed, will provide helpful information for guiding the appropriate use of medications.

FDA guidance development

As drug development science advances, the FDA, in its commitment to reflect experience, new discoveries and the evolution of technology, continues to refine and publish guidance documents and communicate to drug development scientists via reports and websites. In the field of drug–drug interactions, a draft guidance was recently published⁷, which, together with the FDA Drug Interaction website⁸, provides advice for *in vitro* and *in vivo* drug–drug interaction studies (see [Supplementary information S1](#) (box) for a summary of other FDA communications on drug–drug interactions). As well as recommendations on study designs and model decision trees to help determine when to conduct clinical metabolism-based drug–drug interaction studies, suggestions for study design, dosing strategies, and analysis and interpretation of data are included.

The guidance also began to address transporter-related drug–drug interactions, but, at present, the only available transporter information is on P-glycoprotein. The emerging knowledge of the role of transporters in drug absorption and disposition will fill one of the gaps in our understanding of why responses to drugs are so variable.

Harnessing this knowledge, the ITC report published in this issue summarizes the scientific rationale for studies of transporter-based drug–drug interactions in the development of new drugs. This includes an extensive compilation of major human transporters and known substrates and inhibitors, highlighting those that can be used in clinical studies, which will help inform the FDA in its re-issuance of guidance on drug–drug interactions. The article presents decision trees for the evaluation of the potential importance of several emerging key transporters, such as breast cancer resistance protein (BCRP), OATP1B1/1B3 and organic anion and cation transporters (OAT1, OAT3, OCT2), and also provides updated recommendations on P-glycoprotein.

Among the issues discussed in the report is the need for a better understanding of the interplay of drug-metabolizing enzymes and transporters in the disposition of an NME in order to predict potential drug–drug interactions and to elucidate the complex mechanisms that may underlie such interactions. Understanding the effect

of an NME on induction and inhibition of both enzymes and transporters is crucial in determining appropriate labelling language, and in the safe and effective use of the NME. For example, rifampicin, a well-known inducer of drug-metabolizing enzymes (such as cytochrome P450s and UDP glucuronosyltransferases) and transporters (such as P-glycoprotein) has recently been shown to be an inhibitor of OATP1B1, and to increase drug levels of OATP1B1 substrates after a single dose co-administration. This knowledge has added complexity to the interpretation and prediction of drug–drug interaction studies with rifampicin.

The report also touches on the emerging field of genetic polymorphisms in membrane transporters. Genetic polymorphisms in drug-metabolizing enzymes have long been recognized as important determinants of drug levels and consequently drug efficacy and safety. Knowledge of these polymorphisms in the genes that code for drug-metabolizing enzymes such as CYP2D6, CYP2C9 and CYP2C19 is increasingly being incorporated in drug labels. For example, the labelling of tetrabenazine, which was recently approved for Huntington's chorea, includes information about genetic testing for CYP2D6 variants. As we gain more experience and accumulate knowledge of transporter genetics, we expect that drug labels may also include information about genetic polymorphisms in drug transporters.

Conclusions

The ITC report represents an important resource for the FDA to consider in its deliberations of which transporter-related interactions need to be evaluated and described in the labelling of a new drug before marketing. More broadly, consortia such as the ITC provide a new model for compiling and evaluating information about a particular field critical to the development of safe and effective medical products. Notably, the ITC included scientists with expertise in drug development from industry, academic institutions and the FDA. The collective discussions and knowledge of these scientists contributed to the publication of this report, which will help improve drug development, and also contribute to the foundations of personalized medicine: goals that exemplify the vision of the Critical Path Initiative.

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Competing interests statement

The authors declare no competing financial interests.