



April 14, 2008

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RE: Review Submission of the Qualification of Seven Biomarkers of Drug-Induced Nephrotoxicity in rats.

Dear Drs. Dieterle, Mattes, and Sistare:

This letter provides the conclusions from our review of your submission supporting the qualification of seven biomarkers of drug-induced nephrotoxicity in rats. We conclude that:

The urinary kidney biomarkers (KIM-1, Albumin, Total Protein,  $\beta$ 2-Microglobulin, Cystatin C, Clusterin and Trefoil factor-3) are acceptable biomarkers for the detection of acute drug-induced nephrotoxicity in rats and can be included along with traditional clinical chemistry markers and histopathology in toxicology studies.

### **Qualification context in rodent toxicity studies:**

These biomarkers may be used voluntarily for additional evaluation of nephrotoxicity to complement standard data reported in rat safety assessment studies. They provide additional and complementary information to BUN and serum creatinine that correlates with histopathological alterations, which are considered to be the gold standard. The Receiver Operating Characteristic (ROC) analyses showed that some of these biomarkers have better sensitivity and specificity than BUN and creatinine when tested with a limited number of nephrotoxic and control compounds. While further studies are needed to qualify the biomarkers for broader use, the data submitted thus far are sufficient to support the voluntary use in safety assessment testing, in addition to traditional safety markers, as proposed by the Predictive Safety Testing Consortium (PSTC).

Recommended application context for the voluntary use of these urinary biomarkers using the test parameters submitted:

KIM-1, Albumin, Clusterin and Trefoil Factor-3 can be included as biomarkers of drug-induced acute kidney tubular alterations in Good Laboratory Practice (GLP) rat studies used to support clinical trials.

Total Protein,  $\beta$ 2 Microglobulin and Cystatin C can be included as biomarkers of acute drug-induced glomerular alterations/damage and/or impairment of kidney tubular re-absorption in GLP rat studies used to support clinical trials.

FDA agrees with the PSTC proposal that animal model studies should demonstrate early detection of renal injury by use of these novel biomarkers. An understanding of biomarker levels and the reversibility of kidney lesions after drug cessation are required prior to proceeding to clinical studies. In addition, prospective studies are needed to address the correlation between biomarker levels and the evolution of lesions, with secondary confirmation using, where applicable, techniques such as immunohistochemistry and/or in-situ hybridization. Establishment of these correlations on a case-by-case basis is a pre-requisite for further testing of a specific drug in clinical development.

### **Clinical use of these urinary biomarkers:**

While considerable human data exist for some of these novel biomarkers, they are not currently qualified for routine monitoring of drug-induced nephrotoxicity in the clinical setting. In cases where additional evaluation of drug effect on the kidney is deemed useful, the sponsor and FDA's clinical review division will decide on a case by case basis how best to implement the use of these biomarkers in a clinical development program.

Human qualification studies, including studies evaluating the pattern of elevation and the degree and timeframe of reversibility of elevation of these markers after human exposure to known nephrotoxicants such as aminoglycosides, may be helpful in moving these markers into clinical use.

We consider the qualification of novel biomarkers an incremental process and welcome the submission of additional animal and human data to support further application contexts for these biomarkers.

Sincerely,



Janet Woodcock, M.D.  
Director, CDER  
U.S. Food and Drug Administration



John Jenkins, M.D.  
Director, Office of New Drugs, CDER  
U.S. Food and Drug Administration