FDA AND EMEA CONCLUDE THAT NEW RENAL SAFETY BIOMARKERS ARE QUALIFIED FOR SPECIFIC REGULATORY PURPOSES
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Completing another major milestone under their Critical Path and Roadmap to 2010 initiatives, the US FDA and the European Medicines Agency (EMEA) respectively, have concluded that seven urinary biomarkers of kidney injury submitted by the Critical Path Institute's Predictive Safety Testing Consortium (PSTC) are considered qualified for particular uses in regulatory decision-making. This consortium, a pharmaceutical industry public-private partnership led by the non-profit Critical Path Institute (C-Path), submitted the data for these seven urinary proteins (KIM-1, Albumin, Total Protein, β2-microglobulin, Cystatin C, Clusterin, Trefoil Factor-3 to both the FDA and the EMEA in June 2007. The submission included data from PSTC member companies Novartis and Merck, as well as leading scientists at Harvard Medical School and FDA's research laboratories. Additional valuable input came from other PSTC members of the Nephrotoxicity Working Group. The announcements signify the first-ever regulatory biomarker qualification decision under FDA's and EMEA's joint Voluntary eXploratory Data Submission (VXDS) review process. While the FDA's conclusions represent the completion of their process, the EMEA statement provides the CHMP opinion and is being released for a short period of public consultation before the decision is finalized, as per the EMEA's new draft Biomarker Qualification process.

The PSTC was launched by the Critical Path Institute and announced publicly by Secretary of Health and Human Services, Michael Leavitt and FDA Commissioner Andrew von Eschenbach in March of 2006. Once PSTC member scientists evaluated existing data for promising renal safety biomarkers together with regulatory scientists from FDA and EMEA, a scientific plan to address information gaps was developed and agreed upon. Then the experiments were conducted, and the data were analyzed and submitted as a VXDS to the FDA and EMEA with proposals for particular "fit for use" claims for each biomarker. Additional details of the science supporting the utility of these biomarkers in nonclinical and clinical settings, as well as recommended best practices for safety biomarker qualification, and thoughts from the EMEA and FDA on working with the PSTC to evolve biomarker qualification are summarized in several manuscripts to be published in the upcoming months.

The FDA and EMEA opinions acknowledge the benefits from the voluntary use of the new renal biomarkers, in addition to current standard assessments, in pre-clinical rat studies to support regulatory decision-making by improved renal safety detection in the development of new drugs. Some of the biomarkers were found to have better sensitivity and specificity than BUN and serum creatinine when a number of nephrotoxic and control compounds were tested in rats. Both FDA and EMEA also recommend further investigation in clinical studies of these biomarkers, supplementary to the current standards BUN and serum creatinine. Additionally, the FDA has acknowledged that the new renal biomarkers could be used in certain circumstances to enable the regulatory advancement of certain highly promising drugs into human studies – drugs which, in the past, would otherwise have been abandoned because traditionally used markers (BUN, serum creatinine) were not able to detect early-onset renal injury. If a sponsor can show, in the preclinical setting, that the new biomarkers can be used to detect early toxicity, to monitor onset and reversibility, and to manage any potential renal adverse effects of a

new drug with significant therapeutic potential, the sponsor could discuss with the associated FDA review division and the EMEA about engaging in clinical studies using these new biomarkers (in addition to current standard assessments) on a case by case basis. Finally, the FDA and EMEA endorse the submission of additional clinical data, to widen the context of the regulatory clinical use of these biomarkers.

The work of the Critical Path Institute and the PSTC members has also led to refinement in the way FDA, EMEA, and industry manage qualification of safety biomarkers. The concept of 'rolling biomarker qualification' has evolved a step-wise and progressive qualification of new biomarkers for initially specific, narrowly defined regulatory uses while allowing for addition of further significant data over time to a biomarker qualification package that would support broader utility.

This milestone represents a significant advance not just for FDA, EMEA, and the pharmaceutical industry but for public health in general, as new tools to enhance the safety evaluation of promising new medicines are now available for drug development use. The fact that the data submitted was the result of just over a year of consortium work demonstrates not only the value of such collaborative efforts but also the commitment of the member companies* to advance new safety tests. Because of the promise the new markers have shown in the data already generated, further translational studies are planned by the PSTC in order to generate the needed data to expand the qualification of the biomarkers for broader clinical use.

*Members of the Critical Path Institute's PSTC are:
Abbott, Amgen Inc., AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, ClinXus, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson Pharmaceutical Research & Development, LLC, Merck and Co., Inc., Novartis Pharmaceutical Corporation, Pfizer, Inc., Roche Palo Alto, LLC, sanofi-aventis U.S. Inc., Schering Plough Research Institute, a division of Schering Corporation, Wyeth Pharmaceuticals, Inc.