FDA U.S. FOOD & DRUG ADMINISTRATION

Date: November 23, 2016

ATTN: Safer and Faster Evidence-based Translation (SAFE-T) Consortium
Dr. Gary Steven Friedman, Pfizer
Dr. John-Michael Sauer, Critical Path Institute
Martin Shaw, AroCell AB
Dr. Effie Kitsou, Firalis
Dr. Angelika Hoenlinger, Novartis

Subject: Letter of Support for Drug-Induced (DIKI) Renal Tubular Injury Biomarker(s)

Dear Drs. Friedman, Sauer, Shaw, Kitsou, and Hoenlinger,

We are issuing this Letter of Support to the Safer and Faster Evidence-based Translation (SAFE-T) Consortium and Critical Path Institute's (C-Path) Predictive Safety Testing Consortium (PSTC) to encourage the further development and exploratory use of urinary alpha-glutathione S-transferase (α-GST), urinary clusterin (CLU), urinary cystatin C (CysC), urinary Kidney Injury Molecule-1 (KIM-1), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary osteopontin (OPN), urinary albumin (ALB) and urinary total protein (TPRO) as biomarkers of drug-induced renal tubular injury in early clinical trials[1]. This is an expanded list of promising renal toxicity biomarkers from the list included in the Letter of Support issued on August 20, 2014 that encouraged the development of urinary OPN and NGAL as biomarkers of renal toxicity for use in early clinical drug development.

Current clinical monitoring for nephrotoxicity with serum creatinine (sCr) lacks adequate sensitivity for early detection of clinically relevant kidney injury. Unlike sCr, which is a marker of function, some of the candidates (urinary α-GST, CLU, CysC, KIM-1, NGAL, and OPN) are thought to be markers of cellular injury and/or stress in the kidney. Because these biomarkers are localized in different regions of the nephron, the panel is expected to respond to a diversity of nephrotoxicants. It is anticipated that the candidate biomarkers will have the most utility when combined with traditional biomarkers.

OPN is reported to be constitutively expressed in the thick ascending limb of the loop of Henle and distal convoluted tubules in both rodents and humans. OPN has been reported to be upregulated in the kidney in response to certain kinds of tissue stress and during tubular epithelial regeneration. NGAL has been reported to increase within the thick ascending limb of the loop of Henle, distal tubule, and collecting duct in response to nephrotoxic injury in rodents and humans. CLU is expressed in response to kidney injury in the proximal and distal tubules, glomerulus, and collecting duct. KIM-1 mRNA levels are elevated more than any other known gene across multiple species after initiation of kidney injury. α-GST is localized to the proximal renal tubule and is readily released into the urine during injury. CysC is freely filtered at the glomerulus and then reabsorbed by the renal tubular epithelium. Upon kidney injury, impairment of re-absorption in proximal tubules can lead to a several hundred-fold increase in urinary levels of CysC. Both urinary TPRO and urinary ALB are established markers of renal injury of unspecified etiology with TPRO broadly reflective of glomerular and tubular injuries, and ALB more specifically reflecting glomerular

[1] Reference numbers for all biomarkers listed in the letter are provided in the appendix to ensure clarity and allow for consistency in future studies.

injury. As clinically-accepted indicators of onset and progression of kidney damage whose etiology may include nephrotoxic drug exposure, quantitative changes in urinary TPRO / urinary creatinine ratio and urinary ALB / creatinine ratio contextualize changes in standard serum clinical biomarkers and novel urinary biomarkers.

Your exploratory human data suggests that the candidate drug-induced renal tubular injury biomarkers may be more sensitive and specific for the detection of acute kidney injury, especially when used in combination, than traditional means of monitoring for nephrotoxicity. In addition, you observed a rise in most of the candidate biomarkers (urinary α-GST, CLU, KIM-1, NGAL, CysC, and OPN) that preceded a clinically-relevant rise in sCr. Since every biomarker in the proposed panel did not respond to each specific nephrotoxicant, quantitation of changes in a broader urinary biomarker panel will allow drug developers to evaluate potential drug-induced renal tubular injury caused by drugs with different targets for tubular toxicity. To date, these biomarkers have not been definitively demonstrated to detect nephrotoxicity reliably across multiple classes of drugs whose mechanism of drug-induced renal tubular injury span a variety of mechanisms of toxicity. Greater experience in the clinical setting with urinary α- GST, CLU, CysC, KIM-1, NGAL, OPN, ALB, and TPRO is needed to understand the sensitivity and specificity of these urinary biomarkers, when used in conjunction with traditional biomarkers, for drug-induced renal tubular injury. We are aware that there are several efforts to qualify these urinary biomarkers formally for use in clinical trials and we support these development initiatives.

When including novel urinary biomarkers in early clinical studies for the evaluation of a new compound, traditional means of monitoring for nephrotoxicity (e.g. serum creatinine (sCr), serum Cystatin C (sCysC), blood urea nitrogen (BUN), and urinalysis) should also be used. Furthermore, the novel urinary biomarkers could be included in preclinical safety studies in addition to clinical testing to expand the knowledge base. Sponsors should prospectively discuss any application of the novel urinary biomarkers in an early clinical study with the appropriate Office of New Drugs (OND) division in the Center for Drug Evaluation and Research (CDER).

No specific test system or assay validation process is endorsed for the above listed biomarkers. The analytical assay performance characteristics (e.g., quantitative range, limits of the detection, precision, reproducibility, linearity, interference) should be established in advance of use. The sample stability for each of the biomarkers proposed herein should be validated for its intended storage, shipping and use conditions.

We encourage the exploratory use of these urinary biomarkers (α-GST, CLU, CysC, KIM-1, NGAL, OPN, ALB, and TPRO) as biomarkers of renal tubule injury in early clinical trials. The performance characteristics of these biomarkers have not been fully determined and, therefore, biomarker findings should be interpreted in the context of results for traditional biomarkers and clinical and nonclinical findings. We support data sharing and integration of these novel biomarkers across multiple clinical trials. If sponsors intend to include analyses of this panel of urinary biomarkers to support regulatory decision-making for a given investigational new drug (IND) development program, they should prospectively discuss the approach to these analyses with the OND division in CDER.

Any groups (academia, industry, government) that would like to join in this effort or contribute information or data that may be useful to this qualification effort can contact Drs. Gary Steven Friedman (GarySteven.Friedman@pfizer.com), Stefan Sultana (stefan.sultana@novartis.com), Jean- Charles Gautier (Jean-Charles.Gautier@sanofi.com), John-Michael Sauer (jsauer@c-path.org) or via the IMI SAFE-T Website www.imi-safe-t.eu or Critical Path Institute Website (https://c-path.org).

Sincerely,

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Center for Drug Evaluation and Research

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I. Appendix

Reference Libraries

1. UniProt (Universal Protein Resource) is a catalog of information on proteins: http://www.uniprot.org/

2. HGNC (HUGO Gene Nomenclature Committee) is responsible for approving unique symbols and names for human loci: http://www.genenames.org/

Reference Numbers:

Alpha Glutathione S-Transferase
- UniProtKB: - P08263 (GSTA1_HUMAN)
- Gene: GSTA1
- Alternative names: Ligandin, "Glutathione S-Transferase alpha 1",
- HGNC ID: HGNC:4626

Clusterin
- UniProtKB: - P10909 (CLUS_HUMAN)
- Gene: CLU
- Alternative names: "Aging-associated gene 4 protein" "Apolipoprotein J" "Apo-J" "Complement cytolysis inhibitor", CLI, "Complement-associated protein SP-40", "Ku70-binding protein 1" NA1/NA2, "Testosterone-repressed prostate message 2", "TRPM-2", "Sulfated glycoprotein 2"
- HGNC ID: - HGNC:2095

Cystatin C
- UniProtKB: - P01034 (CYTC_HUMAN)
- Gene: CST3
- Alternative names: "Cystatin-3", "Gamma-trace", "Neuroendocrine basic polypeptide", "Post-gamma-globulin"
- HGNC ID: - HGNC:2475

Kidney Injury Molecule 1
- UniProtKB: - Q96D42 (HAVR1_HUMAN)
- Gene: HAVCR1
- Alternative names: "Hepatitis A virus cellular receptor 1, CD365, HAVCR, HAVCR-1, KIM1, "T-cell immunoglobulin mucin family member 1", TIM-1, TIM1, TIMD1
- HGNC ID: - HGNC:17866

Neutrophil Gelatinase-Associated Lipocalin
- UniProtKB: - P80188 (NGAL_HUMAN)
- Gene: LCN2

- Alternative names: NGAL, “25 kDa alpha-2-microglobulin-related subunit of MMP-9”, “Lipocalin-2”, “Oncogene 24p3”, “Siderocalin LCN2”, p25
- HGNC ID: - HGNC:6526

Osteopontin

- UniProtKB: - P10451 (OSTP_HUMAN)
- Gene: SPP1
- Alternative names: “Bone sialoprotein 1”, BSPI, Nephropontin, “Secreted phosphoprotein 1”, SPP-1, “Urinary stone protein”, Uropontin, "Early T-lymphocyte activation 1", ETA-1
- HGNC ID: - HGNC:11255

Albumin (Micro)

- UniProtKB: - P02768 (ALBU_HUMAN)
- Gene: ALB
- HGNC ID: - HGNC:399