FDA Clinical Investigator Training Course: 
Organ Toxicity: Kidney

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Drug-Induced Kidney Injury

A number of offenders

A range of mechanisms and manifestations
Drug development goals

– to ensure the safety of study subjects in clinical trials by enabling the detection of drug-induced kidney injury at an early and reversible stage
– to characterize a drug’s risk of causing clinically significant kidney toxicity

The traditional tool box

– Blood: serum creatinine, estimated glomerular filtration rate (eGFR, typically based on serum creatinine), sometimes serum cystatin C
– Urine: Urine protein:creatinine ratio, urine albumin:creatinine ratio, urine analysis and microscopy
The need for a better tool box

Creatinine’s limitations as a biomarker of kidney injury

Neither sensitive...

Nor specific...

Drugs can affect the tubular secretion of creatinine
- cimetadine, trimethoprim, pyrimethamine, cobicistat, etc.

Drugs can also have hemodynamic effects on renal function that may not reflect injury
- ACEIs, ARBs, diuretics, etc...

Source: The Acute Dialysis Quality Initiative; http://www.adqi.org/
# The quest for a better tool box

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<tr>
<th>Requestor</th>
<th>Qualified Biomarker(s)</th>
<th>Biomarker Description</th>
<th>Abbreviated COU</th>
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<tr>
<td>Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)</td>
<td>Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil factor-3</td>
<td>Urinary nephrotoxicity biomarkers as assessed by immunoassays</td>
<td>Safety biomarker to be used with traditional indicators to indicate renal injury in rat</td>
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<td>Critical Path Institute's Predictive Safety Testing Consortium Nephrotoxicity Working Group (CPATH PSTC-NWG), and Foundation for the National Institutes of Health’s Biomarker Consortium Kidney Safety Biomarker Project Team (FNIH BC-KSP)</td>
<td>clusterin (CLU), Cystatin-C (CysC), Kidney Injury Molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and osteopontin (OPN)</td>
<td>Urinary nephrotoxicity biomarker panel as assessed by immunoassays</td>
<td>Safety biomarker panel to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers</td>
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https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers
Closing Comment

• **No one size fits all** for: monitoring for drug induced kidney injury; setting exclusion criteria; or defining stopping rules for study drug administration to mitigate risk

• **If there is concern that a drug may cause kidney toxicity** *(based on preclinical data, experience with the larger pharmacologic class or a signal that emerges during drug development):*
  
  o Work with an expert in drug-induced kidney injury to optimize the design of your development program to mitigate risk to study subjects and adequately characterize the risk
  
  o Include such an expert on the Data Safety Monitoring Board overseeing your trial(s)