CHEMISTRY and CHEMICAL BIOLOGY

McMaster University

27 September, 2018

Dr. Phillip Steindel
Review Editor, JoVE

Re: Manuscript Submission: "High Throughput and Comprehensive Drug Surveillance using Multisegment Injection-Capillary Electrophoresis-Mass Spectrometry (JoVE58986)

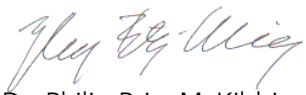
Dear Dr. Steindel,

We wish to re-submit our revised manuscript to *JoVE* as an article (JoVE58986) that describes an innovative method for *high throughput and comprehensive surveillance of drugs of abuse* (DoA) without complicated sample handling when using multisegment injection-capillary electrophoresis (MSI-CE-MS). This is urgently needed given a *global opioid drug crisis and its impact on public health*, including an alarming number of overdose deaths attributed to synthetic opioids and other addictive psychoactive medications. We have included a highlighted version of our manuscript indicating all changes made, as well as a detailed response to reviewers/editors critiques in our submission.

Currently, a two-tiered strategy is used for urine drug testing based on a primary screen using immunoassays followed by confirmatory testing by more specific yet lower throughput GC/MS and increasingly LC-MS/MS methods. However, this screening algorithm is prone to both false positives and false negatives due to the cross-reactivity and poor sensitivity of antibody reagents for many classes of DoA in human urine. Additionally, conventional GC-MS and LC-MS methods have limited sample throughput for resolving a chemically diverse range of DoA and their metabolites due to times required for elution and column conditioning. Herein we report an improved method for drug surveillance using MSI-CE-MS that is an extension to our recently published work (*Anal. Chem.* **2017**, 89,11853). In this contribution, we focus on describing a **detailed protocol** for routine drug screening by MSI-CE-MS using a **modified methodology** to improve resolution of complex drug mixtures (isobars/isomers) in authentic urine samples from a cohort of **clinically depressed patients**. We also demonstrate unambiguous identification and quantification of diverse classes of DoA as required for confirming patient drug adherence and potential drug misuse/substitution based on their known prescription.

In summary, we anticipate that our manuscript will appeal to a broad audience while offering a powerful new solution for systematic drug surveillance for an alarming array of illicit drugs, prescription medications and over-the-counter drugs prone to abuse/misuse and inadvertent overdose. We hope that publishing in JoVE will allow for better translation of our methodology to other research laboratories in academia, as well as commercial forensic toxicology/therapeutic drug monitoring laboratories.

Sincerely,



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