Deuterated Therapeutics:
Forensic Toxicology Consequences

To the Editor:

The toxicology community should be aware that pharmaceutical companies are developing deuterated analogues of therapeutic agents, purported to have improved margins of safety and reduced potential for drug interactions, according to a recent report (1). According to the article in *Nature*, companies are “snapping up intellectual property rights” on many of the modified drugs.

Earlier this year, Concert Pharmaceuticals (Lexington, MA) reported the results of a phase I clinical trial of deuterated paroxetine. Paroxetine (Sertraline) was first marketed by GlaxoSmithKline in 1992. According to a study of 94 women, the deuterated drug was less susceptible to drug interactions when co-administered with another drug (dextromethorphan), also metabolized by the CYP2D6 isoenzyme. Other companies have followed suit. Auspex Pharmaceuticals (Vista, CA) completed phase I clinical trials on SD-254, a deuterated analogue of venlafaxine (Effexor), initially developed by Wyeth in 1993. According to the report, the deuterated venlafaxine had fewer side effects and a longer half life. According to their website, Auspex develops next-generation medicines with improved safety and performance and has pioneered the targeted application of deuterium chemistry to clinically validated drugs (2). Auspex has filed patent applications on hundreds of novel therapeutics based on clinically validated drugs. These include atomoxetine, duloxetine, fluoxetine, hydrocodone, ibuprofen, oxycodone, paroxetine, venlafaxine, and zolpidem, to name a few (3). In May 2009, Concert Pharmaceuticals announced two U.S. Patents (7,514,068 and 7,528,131) for deuterium-labeled rimonabant and mosapride, respectively. They have filed over 100 patents to date and “believe that these two patents are the first of many that will be granted on compounds derived from [their] deuterium chemistry platform” (4). The press release announcing the two patents states that “Concert’s approach leverages known activity and safety of existing drugs to reduce time, risk and expense to drug research and development”. According to a June 2009 news report and press release, Concert Pharmaceuticals, Inc. and GlaxoSmithKline will collaborate to develop and commercialize deuterated drugs in a deal worth $1 billion (5,6).

The article in *Nature* speculates that just as pharmaceutical companies often include active isomers and specify chirality in their patents, they may also include deuterated analogues to protect their intellectual property and drug discover costs (1). Proponents of this new approach explain the difference in pharmacological properties that are due to deuterium’s ability to form stronger bonds than hydrogen.

Although toxicologists and the scientific community at large support and encourage research to develop safer and more effective drugs, we must be mindful of the potential consequences. Virtually all accredited forensic toxicology laboratories utilize deuterated analogues for qualitative and quantitative drug determination. Widely accepted forensic toxicology guidelines recommend the use of deuterated drugs wherever possible (7). The introduction of deuterated therapeutics into the mix could have serious analytical consequences: absence from commercial and commonly used mass spectral databases, development of new analytical methodology for targeted detection, establishing multiple methods for a variety of deuterated analogues, re-evaluation of interferences, possibly invalidating existing standard operating procedures, and compromising the use of existing deuterated internal standards that have widespread use. Aside from the analytical variables, the pharmacological consequences could be daunting. Forensic toxicologists are already faced with numerous interpretive challenges in both antemortem and postmortem casework. To factor in potential pharmacokinetic and pharmacodynamic differences within-drug for the different deuterated therapeutics would require scientific study on a gargantuan scale. Some of these concerns were addressed in a follow-up article in *Nature*, wherein forensic toxicologists voiced a variety of concerns (8).

Furthermore, it would be particularly troubling if the surge in patenting deuterated analogues were to restrict access to these compounds. The analogues would have to be produced under license and this could have serious consequences in terms of cost and commercial availability. Some laboratories already limit their use of deuterated internal standards because they are more costly compared to non-deuterated alternatives.

Forensic toxicologists are stakeholders and advocates of drug discovery and the development of therapeutics with improved margins of safety. As practitioners in behavioral and postmortem toxicology laboratories, we are acutely aware of the human consequences of drug use, in both medical examiner and human performance casework. We support the development of new research.
and safer drugs in a responsible fashion. Widespread patenting of deuterated analogues, however, in the hope that they have sufficiently “new” or different properties to satisfy the “non-obviousness” requirements of the U.S. Patent and Trademark Office, would have serious consequences. Publication of clinical data in peer-reviewed scientific journals will help make the case for the introduction of deuterated therapeutics for the most promising candidates. However, patenting these substances en masse for profit-making purposes rather than the advancement of medicine could have severe and unintended repercussions for forensic laboratories.

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References