January 23, 2020

Dr. Janet Woodcock, M.D.,
Director, Centers for Evaluation and Research

Dr. Peter Stein, M.D.
Director, Office of New Drugs

U.S. Food and Drug Administration
10903 New Hampshire Ave
White Oak Building 51
Silver Spring, MD 20993-0002

Dear Drs. Woodcock and Stein,

As you know, over the last year Vanda has strived to identify technologies and means that can improve upon the prediction of toxicity of human drugs. It is well understood that the current framework of predictive toxicology is not adequate to ensure human safety and that efforts are under way within the government, academia and the industry to develop human relevant tests with high predictive power.

Our research has compelled us to alert you to our findings that we believe are actionable today. We suggest a path that you may want to consider as you contemplate the Agency's framework on drug safety, both for new drugs as well as drugs that already approved. You are well aware that drug-induced liver injury (DILI) is a serious and real threat to patients, accounting for 13% of acute liver failure and 15% of liver transplantations (Ostapowicz et al., 2002; Russo et al., 2004). The current system of detection that utilizes repeated dose animal toxicology testing has proven not adequate to detect and anticipate human liver toxicity (Senior, 2006).

The tragedies of fialuridine and troglitazone are a two of the very well known examples where failures of the current predictive toxicology system resulted in loss of human life and/or severe injury. In both of these cases, retroactive reviews failed to identify a human error or omission of collection of preclinical scientific information that could have prevented these tragedies at that time (Institute of Medicine, 1995; Watkins, 2005). Both these events happened more than 20 years ago. In the meantime, the human genome has been sequenced, and we are living in a renaissance period of scientific advances in human biology.

The Institute of Medicine (IOM) committee that reviewed the fialuridine tragedy made a profound concluding statement that is worth revisiting: *"To summarize, on review of the fialuridine tragedy, the IOM committee finds no evidence of negligence or carelessness on the part of the investigators or sponsors. The committee is not aware of any preclinical tests that could have been done to anticipate this unfortunate outcome."* (emphasis added, Institute of Medicine, 1995). More than 20 years later and through the tireless work of many, preclinical tests are now available that could have predicted both the fialuridine and the troglitazone catastrophes.

Especially, I want to call your attention to two technologies that experts in the field would agree are adequately validated in both reproducibility and predictive power in the context of liver injury; 3-D spheroids with primary human hepatocytes and the Emulate Organ-on-Chip platforms. In the 2018 Vorrink paper, they *"evaluated the hepatotoxicity of 123 drugs with or without direct implication in clinical DILI events. Importantly, using ATP quantifications as the single endpoint, the model accurately distinguished between hepatotoxic and nontoxic structural analogues and exceeded both sensitivity and specificity of all previously published in vitro assays at substantially lower exposure levels, successfully detecting 69% of all hepatotoxic compounds without producing any false positive results (100% specificity)*" (Vorrink et al., 2018).

Attached to this note you will find additional publications that highlight the properties and capabilities of these technologies (Bell, 2016, 2017, and 2018; Jang et al., 2019; Vorrink et al., 2018). No technology is perfect but these technologies will certainly be a leap forward in predictive toxicology as they would have anticipated the fialuridine tragedy and most likely prevented the death and injury of hundreds or thousands of Americans treated with troglitazone (Institute of Medicine, 1995; Watkins, 2005).

We are aware that the FDA has a significant investment in this area, especially in the context of the Tox21 initiative and FDA researchers are familiar with these technologies. As with any new technology, there is a period of evaluation and hesitation, however, we believe that the moment has come for the FDA to lead and encourage investigators and the pharmaceutical industry to expediently adopt such technologies and with no delay evaluate new drugs as well as approved drugs and provide the data to the public. Your leadership is necessary to ensure that we can still say with the same confidence what the fialuridine IOM committee concluded: *"(we are not) aware of any preclinical tests that could have been done to anticipate this unfortunate outcome"* (Institute of Medicine, 1995). Hopefully, the expedient adoption and continuous development of new technologies will minimize and avert any such tragic incidents in the future.

In our quest to identify better predictive technologies, Vanda has scouted the worldwide literature and talked with experts here in the U.S. and abroad. The experts exist and are ready to support such an effort, and everyone is waiting for the FDA's leadership to proceed. Our evaluation suggests that any delay in adopting these technologies may unnecessarily cost human lives. Vanda has already initiated a project to evaluate all Vanda compounds, both in the market as well as those in development, with these technologies.

Vanda is willing to facilitate a public-private partnership to ensure the expedient adoption of these technologies and the testing of old and new drugs alike.

Given the significance of this proposal for the U.S. public at large, I have taken the liberty to copy FDA Commissioner Hahn on this note. I hope that you will consider this proposal with urgency in the service of the American public whose welfare we are both committed to serve.

Sincerely,

/s/ Mihael H. Polymeropoulos, M.D.

President and Chief Executive Officer
Vanda Pharmaceuticals Inc.

CC:
Dr. Stephen M. Hahn, Commissioner
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