Columbia University
IN THE CITY OF NEW YORK

Department of Chemistry

February 28, 2018

The Honorable Michael Burgess
US House of Representatives
2336 Rayburn HOB
Washington, D.C. 20515

The Honorable Gene Green
US House of Representatives
2470 Rayburn HOB
Washington, D.C. 20515

Dear Chairman Burgess and Ranking Member Green,

I am writing to express my concerns in regard to the ‘‘Stop the Importation and Trafficking of Synthetic Analogues Act of 2017” (“SITSA Act”; H.R. 2851) and respectfully offer my recommendations for improving this proposed legislation. I am a medicinal chemist by training and serve as an Associate Research Scientist at Columbia University, where I pursue multiple lines of research in the broad areas of neuroscience and psychoactive drugs, with a specific focus on the design, synthesis, and study of novel opioid receptor modulators. Myself and colleagues pursue the key long-term goal of applying our work in studying such chemical compounds to positively affect human health, including through the development of new therapeutics for treating psychiatric and physical pain disorders.

To achieve this goal, we also collaborate with scientists across the United States and internationally and thus, have broad exposure to the promise and challenges of this exciting research area. I also serve as CEO and co-founder of a small startup company working to translate our discoveries from the laboratory bench to the doctor’s toolbox. The nature of our work often requires the study of controlled substances, whether as controls in experiments, starting points for modification and improvement, or potential therapeutics in their own right. Accordingly, I feel I am well qualified to speak on both the promise and importance of my chosen field’s work and also the challenges that regulatory controls often place in the path of these pursuits.

Before proceeding with a specific discussion of the SITSA Act and its negative implications for scientific research as currently written, I feel it is important to review the history of these issues and existing problems with the regulatory framework around controlled substances. As the members of the committee are aware, the Controlled Substances Act (CSA) currently regulates a number of psychoactive compounds as Schedule I drugs. This most restrictive schedule of the act places severe compliance burdens on legitimate researchers who seek to study these substances and unlock their medicinal potential.

For example, prospective Schedule I licensees must submit detailed research plans, permit inspections of their facilities, and obtain specialized storage equipment (lockboxes and the like, in some cases with direct alarms to local law enforcement), often at significant cost. Such burdens are often further complicated by state and local licensing requirements. Further, the existing compliance requirements also dramatically curtail scientific collaboration because most laboratories or commercial vendors with which a Schedule I licensee may wish to collaborate, will not hold the necessary licenses, nor will they be willing or able to obtain them. This problem has become particularly acute in the increasingly interdisciplinary world of modern biomedical research, where collaborative teams are essential to major discoveries. These many challenges have historically resulted in very few researchers being able or willing to obtain such Schedule I licensing. The resulting chilling effect on basic and translational research with Schedule I substances has been dramatic and long lasting and cannot be understated.

Further, the current regulatory requirements do not make sense from a practical perspective and do not serve the purpose of the CSA, ostensibly to protect the public from exposure to harmful psychoactive

substances. The requirements for Schedule I licensing are significantly more stringent than those for substances in Schedules II-V, despite the fact that many substances in these less restrictive schedules have a potential for abuse and diversion as great, or greater than, many substances listed in Schedule I. It should further be noted that although stringent precautions are certainly warranted for commercial facilities manufacturing or distributing large quantities of controlled substances, it is my respectful opinion that they go above and beyond what is necessary in the context of basic research, where the quantities of material required are extremely limited. Research with cells and/or animals typically requires a quantity of material far below that which could be credibly claimed to have a risk for diversion to the illicit market. In fact, the quantity of material required is in many cases too little to have a measurable effect on even a single human being. Considering this extremely limited risk of diversion or exposure to the public via legitimate scientific research channels, it seems unreasonable to impose restrictions which unnecessarily undermine the ability of the scientific community to study Schedule I compounds.

Lastly, we must consider the immense potential benefits that research on Schedule I substances may ultimately have for medicine, particularly in the area of mental health. Simply because a compound is currently found in Schedule I does not mean it can never be found to have medical benefits when used appropriately and with care. Despite the challenges of working with Schedule I substances, some in the research community have persisted and are demonstrating exciting efficacy for Schedule I drugs in treating a number of serious and underserved medical disorders.

For example, MDMA, the active component of "ecstasy", is currently in Phase III clinical trials for the treatment of post-traumatic stress disorder and has been granted Breakthrough Therapy Designation by the Food and Drug Administration (FDA). Likewise, psilocybin, the active component of "magic mushrooms", has demonstrated efficacy in treating cancer-associated depression, and a little-known compound derived from an African plant, ibogaine, has shown great promise in treating drug addiction (in trials outside the US due largely to regulatory challenges). Further, it should be remembered that even heroin is an effective and safe analgesic for severe pain when used under a doctor's care, and in fact has been used in the United Kingdom for this purpose for decades. Accordingly, a substance's inclusion in Schedule I should not immediately dismiss it as a potential therapeutic.

I am hopeful that the members of the committee will agree that scientific research with such substances must be allowed to continue with limited obstruction when at all possible, such that new medicines may one day be delivered to patients. Although progress has been made, it has been dramatically slowed due largely to our existing regulatory framework and the negative stigma automatically associated with compounds placed in Schedule I.

Given these existing challenges with research on Schedule I compounds, the SITSA Act as written is particularly concerning, as it presents new barriers to scientific research with controlled substances and continues the trend of ignoring the input of the scientific community in regulatory decisions.

First, the SITSA Act creates a new drug schedule, Schedule A, to which compounds may be added with no well-defined evidentiary standard. Specifically, the act requires that a substance to be added to Schedule A have (1) a chemical structure that is *substantially similar* to the chemical structure of a controlled substance in any existing schedule and (2) an actual or *predicted* stimulant, depressant, or hallucinogenic effect on the central nervous system (emphasis mine).

From the expert perspective of a chemist or pharmacologist, both of these requirements are excessively ambiguous. It is not clear how much deviation in chemical structure is required before a

chemical compound is no longer "substantially similar", nor *could* such a requirement be clearly defined and applied generally across all possible cases given the vast structural variability of drug-like compounds. This is well evidenced by the observation that the concept of "structural similarity" is frequently litigated in US courts in the context of pharmaceutical patent disputes, where each case must be carefully considered by experts and decided on its individual merits.

Similarly, the ability to *predict* a psychoactive effect of a given chemical compound based *solely on its chemical structure*, is *extremely limited.* It is well known to a practicing medicinal chemist that even small changes to the structure of a chemical compound, in some cases as small as the addition or removal of a single atom, can change the potency of that compound's effect by 100-fold or more. Accordingly, an unstudied compound, although appearing largely similar in chemical structure to a known psychoactive drug, may in fact be completely inactive. Thus, to place regulatory controls on a substance based merely on predicted effect is unwarranted at best, and at worst, scientifically negligent.

Second, the SITSA Act specifies that the listing of a substance in Schedule A (either temporary *or permanent*) is at the sole discretion of the Attorney General and requires no input from the scientific community at large, nor the leading federal agency dedicated to the study of drug abuse issues, the National Institute on Drug Abuse (NIDA). Further, temporary scheduling orders under this new statute would not be subject to judicial review. It is unsettling that a law enforcement agency (the Department of Justice) would be solely entrusted to make a complex regulatory decision requiring careful and complex scientific analysis, and having far-reaching consequences for not only scientific research, but public health and criminal justice, without the input of all stakeholders.

Further, the proposed definition of Schedule A and procedures for listing in said schedule largely circumvent and render meaningless the existing regulatory framework and controls of the CSA. Because the SITSA Act would allow the Attorney General to unilaterally place new substances into Schedule A with little if any evidentiary standard, including both temporary and permanent scheduling actions, which can be initiated simultaneously, there is no longer any reason to utilize the existing (if imperfect) scheduling procedures of the CSA. Existing procedures at least require presentation of *some* evidence demonstrating abuse liability, extent of abuse, or adverse public health consequences for a proposed controlled substance (e.g. 8-factor analysis) and include clear pathways for input from federal agencies with specialized medicinal and scientific expertise (e.g. the FDA and NIDA). If a new, easier, and unilateral pathway is now available, there will be no incentive for the Attorney General to proceed through the more rigorous scheduling procedures currently codified in the CSA.

Lastly, the SITSA Act imposes substantially the same regulatory requirements upon legitimate use (e.g. scientific research) of Schedule A substances as those currently imposed for Schedule I substances. Thus, placement of a substance into Schedule A is likely to have a chilling effect on scientific research with said substance identical to that of placing it in Schedule I, which I hope the members of the committee will agree, has historically been substantial. This is unreasonable given both 1) the substantially lower standard for placing a new chemical substance into Schedule A as compared to Schedule I and 2) as noted above, the high possibility which exists for substances to be placed into Schedule A without any actual evidence of abuse liability or danger to public health.

The danger to the scientific enterprise is further exacerbated by the observation that given the lower evidentiary standard of Schedule A listing, as discussed above, such procedures are likely to be the most frequently utilized for scheduling of new substances from this point forward, and therefore preclude an ever-growing list of biologically interesting compounds from scientific study. Further, although I note that

the legislation has admirably precluded individuals merely in possession of Schedule A controlled substances from criminal and civil sanctions, this exemption will not be expected to protect many scientific researchers. Given that most substances to be listed under Schedule A are expected to be novel compounds with little history of use or study, it is likely that they will not be commercially available to researchers for purchase (especially given the new regulatory requirements for commercial manufacturers). Accordingly, chemists will need to synthesize these compounds in the laboratory (in limited quantities) to permit study and thereby, the activities in many research laboratories would by necessity extend beyond simple possession. Thus, a "possession exemption" as written is not enough to protect the scientific enterprise.

Such regulatory policies are unfortunate not only in their long-term negative implications for development of new therapeutics, but also for their immediate negative consequences for our understanding of little-studied chemical entities. If the Attorney General or another regulatory agency genuinely believes that a new substance, which in many cases has never been the subject of rigorous scientific study, poses a danger to the public, then research must be allowed to continue such that the effects and risks of said substance may be understood. As the committee is well aware, legislation is unlikely to entirely remove any controlled substance from the illicit market or completely prevent its exposure to the public. Accordingly, the physiological and behavioral effects of new and emerging drugs of abuse must be studied to provide reliable information to physicians and public health agencies attempting to cope with the real-world consequences of their use.

In light of the above concerns with the SITSA Act as written, I would like to respectfully propose practical solutions that would provide greater scientific rigor in the evaluation of proposed controlled substances and limit the regulatory burden for legitimate scientific researchers intending to study such substances, while concurrently having little or no impact on the effectiveness of the proposed act to serve its intended purpose. It is my understanding that such intent is to improve the ability of law enforcement to respond rapidly to newly identified harmful substances on the illicit market, with a particular emphasis on interdiction of illegally imported substances and disruption of moderate- or large-scale domestic and international drug trafficking operations. Accordingly, the following recommendations should be considered in the context of this goal and it should be recognized that they will present little or no impediment to its achievement.

First, the SITSA Act should require better evidentiary standards to establish that a proposed controlled substance has an *actual*, *not merely predicted*, psychoactive effect before scheduling can proceed. Such standards might include, at a minimum, 1) radioligand binding studies and functional assays in cells to demonstrate that a given compound has an effect on a central nervous system receptor activated or blocked by known scheduled substances and a potency similar to or higher than compounds having known effects in humans and 2) effects in classical rodent assays of abuse liability like conditioned place preference or self-administration, again with a potency similar to or higher than compounds having established effects in man. Federal scientific agencies (e.g. NIDA) already maintain laboratories or contract with academic institutions capable of quickly and easily performing such studies, so lack of resources should not be an excuse for more rigorous profiling of unknown substances before regulatory action is taken. For example, the Psychoactive Drug Screening Program funded by the National Institute of Mental Health provides *rapid* screening for binding and functional activity of novel compounds at central nervous system receptors.

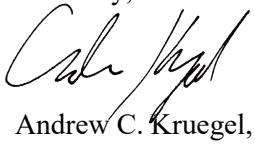
Second, the SITSA Act should *require* the concurrence of both federal scientific (e.g. NIDA) and medical agencies (e.g. FDA), or an independent scientific body, that a proposed substance meets the standards for Schedule A control (ideally amended as above).

Third, the SITSA Act could greatly minimize the impact on the scientific research community through two mechanisms, 1) making the regulatory requirements for the use and handling of Schedule A substances more consistent with those for substances in Schedules II-V, which are less onerous, and 2) instituting exempt quantities below which regulatory requirements would not apply. Such exemption amounts (the maximum to be possessed/used/manufactured by a given laboratory/individual at any given time) would protect in a clearly defined way not just possession, but also laboratory scale manufacturing, structural modification, or other uses provided that the total quantity at issue was below the exemption amount.

For substances of well-defined potency, an exempt quantity could be set at some small multiple (e.g. 10-fold) of the dose required (or reasonably expected) to elicit an observable psychoactive effect in a human being. For substances where there is no or little information about their pharmacology or potency, a default exempt quantity could apply until such information was obtained. Exempting such limited quantities would permit the vast majority of early stage research in cells and animals to continue unhindered, while presenting extremely limited risk of diversion to illicit markets or risk to public safety. It cannot reasonably be argued that a handful of scientific laboratories across the entire country, each possessing at most a few human-equivalent doses of a Schedule A substance at any given time, could reasonably serve as a viable illicit market for such substances or expose the general public to any appreciable risk of exposure. Further, the existence of such exempt quantities would not interfere with the broader intent of the act whatsoever, especially considering that the act already exempts possession of Schedule A substances from regulatory control, clearly signaling its intent to focus on disruption of moderate- or large-scale drug trafficking operations.

It is my hope that through the above discussion you will understand the challenges the research community has faced both historically and will face in the future, with regard to regulation of controlled substances. I hope you will also agree that careful, legitimate research on controlled psychoactive substances holds great promise for improving human health, particularly in the area of mental health, where improvements to the standard of care are so desperately needed. In light of this, I respectfully ask that you consider my proposals for improving the SITSA Act to limit its detrimental affect on scientific research.

Sincerely,



Andrew C. Kruegel, PhD
Associate Research Scientist
Columbia University
New York, NY 10027