U. S. Department of Justice
Drug Enforcement Administration
800 K Street, NW
Suite 500
Washington, DC 20001

www.dea.gov

The Honorable Patti B.Saris
United States Sentencing Commission
One Columbus Circle, NE
Washington, DC 20002

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Dear Judge Saris:

Once again, thank you for giving the Department of Justice and the Drug Enforcement Administration (DEA) an opportunity to present views and testimony on the appropriate sentencing comparison for N-benzylpiperazine (BZP) and the "safety valve" application to precursor chemicals. The following is in response to questions posed by the Commission.

1. DEA Statements Comparing BZP to Amphetamine.

For the purpose of sentencing, DEA has taken the position that BZP is ten times less potent than amphetamine. DEA has also stated in its drug scheduling documents that BZP is twenty times less potent than amphetamine. In addition, both DEA's Notice of Proposed Rulemaking correction (75 FR 47503) and its Final rule correction (75 FR 47451), which were published on August 6, 2010, stated the following: "BZP is 10 to 20 times less potent than amphetamine." All of these statements are correct. For the reasons stated below, we are recommending that BZP is ten times less potent than amphetamine for the purpose of sentencing.

2. Available Research Regarding the Potency of BZP Compared to Amphetamine

Relevant research includes studies investigating the effects of BZP in both animals and humans. The difference in the pharmacological potency (ten times less potent versus twenty times less potent) can vary depending upon the experimental conditions of the study. For example, Bye *et al.* (hereafter the Bye study),[1] which used drug-naive subjects, studied the effects of BZP at 20 mg, 50 mg, and 100 mg and of dexamphetamine (amphetamine) at 1 mg, 2.5 mg, 5.0 mg, and 7.5 mg on performance tests (e.g., auditory vigilance test, hand steadiness test, addition test) measuring amphetamine-like activity. The threshold dose (or the lowest dose tested) that produced statistically significant effects in performance for BZP was 20 mg and for dexamphetamine was 1 mg which calculates to a 20-fold difference in potency of BZP compared to amphetamine. In another published clinical study, Campbell *et al.* (hereinafter referred to as the Campbell study),[2] (using subjects with a history of amphetamine dependence), examined the subjective, behavioral and autonomic (*e.g.*, blood pressure, pupil size, heart rate) effects of 100 mg BZP, 10 mg

[1] C. Bye, A. Munro-Faure, A. Peck, *et al.*, 1973, A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests, European Journal of Clinical Pharmacology, 6(3): 163-169.
2 H. Campbell, W. Cline, M. Evans, *et al.*, 1973, Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts, European Journal of Clinical Pharmacology, 6(3): 170-176.

dexamphetamine and a placebo and found that the BZP was approximately ten times less potent than amphetamine.

In addition to the experimental conditions, the species used can also influence the potency estimates. In a study that measured behavioral responses of BZP in animals,[3] Fantegrossi *et al.* demonstrated that BZP fully substituted for dexamphetamine in monkeys that were trained to discriminate dexamphetamine from saline indicating that BZP has amphetamine-like effects. The study reported that ED50 values (or the dose producing 1/2 maximal activity) for BZP and dexamphetamine were 9.3 mg/kg and 0.2 mg/kg, respectively. This calculates to a 46 fold difference in potency of BZP compared to amphetamine.

There are more recently published clinical studies that have investigated the effects of BZP in humans. However, it is important to note that none of these studies directly compared the effects of BZP to those of amphetamine or 3,4-methylenedioxymethamphetamine (MDMA). One study[4] investigated the pharmacological effects of BZP alone and two studies[5,6] investigated the effects of BZP in combination with 3-trifluoromethylphenylpiperazine (TFMPP). Lin *et al.*[7] investigated the effects of party pills containing BZP in healthy female volunteers (hereinafter referred to as the "Lin I study"). In the Lin I study, subjects were given either BZP (200 mg) or a placebo and subjective effects were assessed using standardized rating scales. The Lin I study concluded that the physiological and subjective data indicated a clear similarity between the effects of BZP and those of other common stimulants such as amphetamine and MDMA. In a separate study, Lin *et al.* [8] investigated the effects of party pills containing BZP in combination with TFMPP (100 mg BZP and 30 mg TFMPP) compared to placebo in healthy males (hereinafter the "Lin II study"). The Lin II study concluded that BZP in combination with TFMPP induced subjective effects similar to those of amphetamine and MDMA. Similarly, Thompson *et al.* (hereinafter referred to as the "Thompson study")[9] found that the combination of 300 mg BZP and 74 mg TFMPP also has amphetamine-like effects. While these studies used methods that are well-validated and widely used to assess the subjective effects of BZP in humans, these studies lacked direct comparators in that subjects were not tested with MDMA or amphetamine. Therefore, the potency of BZP compared to amphetamine or MDMA cannot be determined from these studies.

3. Justification for Using a Potency Difference of 10 Fold Rather Than 20 Fold

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3 W.E. Fantegrossi, G. Winger, J.H. Woods, *et al.*, 2005, Reinforcing and discriminative stimulus effects of 1-benzylpiperazine and trifluoromethylphenylpiperazine in rhesus monkeys, Drug and Alcohol Dependence, 77(2): 161-168.

4 J.C. Lin, N. Bangs, H. Lee, *et al.*, 2009, Determining the subjective and physiological effects of BZP on human females, Psychopharmacology, 207(3): 439-446.

5 I. Thompson, G. Williams, B. Caldwell, *et al.*, 2010, Randomised double-blind, placebo-controlled trial of the effects of the 'party pills' BZP/TFMPP alone and in combination with alcohol, Journal of Psychopharmacology, 24(9): 1299-1308.

6 J.C. Lin, R.K. Jan, H. Lee, *et al.*, 2011, Determining the subjective and physiological effects of BZP combined with TFMPP in human males, Psychopharmacology, 214(3): 761-768.

7 Ibid. 4

8 Ibid. 6

9Ibid. 5

DEA has considered all of these studies in taking the position that BZP is ten times less potent that the same amount of amphetamine. As previously stated, the pharmacological potency data can vary depending upon many factors such as the effect measured, the experimental conditions, or the species used. Of the studies discussed above, there are only two published clinical studies that directly compared the effects of BZP to those of amphetamine, the Bye study and the Campbell study. The Bye study used drug-naïve normal human volunteers with no prior history of amphetamine abuse while the Campbell study used former amphetamine addicts as their test subjects. Among these two clinical studies, the Campbell study is the most relevant and appropriate in assessing the potency difference between BZP and amphetamine with regard to their abuse liability. Because amphetamine-experienced subjects are familiar with its effects, they are likely to be more reliable in detecting its psychoactive effects and in providing ratings of drug experiences as compared to amphetamine-naive subjects. Further, the use of drug-naïve subjects has an additional limitation of introducing a high risk of false negative results. Thus, drug experienced users would be able to better compare the effects of an unknown drug (i.e., BZP) to that of a drug that they are familiar with (i.e., amphetamine). In addition, a comparison of the subjective effects is a better predictor of abuse liability (the likelihood that the substance will be abused) than measuring other effects. Subjective effects were specifically evaluated in the Campbell study. The Bye study focused more on an evaluation of the autonomic/somatic effects (e.g., cardiovascular effect- heart rate, blood pressure, effects on pupils – dilation, effects on vigor).

While it is accurate that BZP is 10 to 20 times less potent than amphetamine, DEA believes that abuse liability-related differences in potencies are the most appropriate factors for determining the dose equivalencies for the purpose of sentencing. Thus, the information from the Campbell study was used in providing the present recommendation for the potency difference between BZP and amphetamine. The Campbell study compared the subjective effects (subjective effects were assessed from psychiatric rating scales and subject and physician questionnaires) of 100 mg BZP, 10 mg dexamphetamine and a placebo and found that BZP was approximately 10 times less potent than amphetamine.

4. Use of BZP Actual Equivalency Rather Than Mixture.

DEA's recommendation that the Commission use the marijuana equivalency of BZP ("actual") instead of a mixture is based on studies that demonstrated the amphetamine-like effects of BZP using the actual amounts of the substances (*i.e.*, 100 mg BZP and 10 mg amphetamine). This recommendation is appropriate for cases in which the actual content of BZP is quantified. However, determining the actual quantity of BZP in materials may pose a burden on law enforcement laboratories regarding the amount of work required to evaluate the purity of substances when calculating the actual quantities of BZP in seized materials. In light of this, in cases where BZP is not quantified, DEA is not opposed to the use of the marijuana equivalency of BZP mixture which would be 1 g of BZP is equivalent to 200 g of marijuana ($1/10^{th}$ of amphetamine's marijuana equivalency). This equivalency is derived using the established equivalency of 1 g of amphetamine mixture being equal to 2000 g of marijuana. When BZP cannot be quantified, law enforcement laboratories will use confirmatory analyses[10] (a qualitative method to determine the presence of a

[10] BZP is routinely encountered in the clandestinely produced tablet form and the tablet is analyzed for the presence of BZP and confirmed by comparing the results to a laboratory standard of BZP.

substance by comparison to a substance of known identity, in this case) and the total weight of the seized materials to calculate the marijuana equivalency instead of determining the actual quantity of BZP in the seized materials.

5. The Commissioners' Discussion of DEA Affidavits

During the hearing, Commission members referred to certain DEA affidavits. DEA has been asked to address these affidavits in this supplemental response. DEA is unable to identify the affidavits at issue. If the Commission is able to provide a copy of the affidavits, DEA will review them and provide the requested response.

Sincerely,

Scott Masumoto
Assistant Special Agent in Charge
Washington Division