Federal Sentencing Guidelines Commission
Hydrocodone Hearing- March 12, 2015
Written Response to Proposed Amendments

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Actual Weight Versus Unit

The proposed amendment to base hydrocodone offenses on actual weight of the hydrocodone alone is appropriate (p. 56 Guidelines). From a pharmacological perspective, hydrocodone is comparable to oxycodone with respect to its psychoactive properties. The current approach to oxycodone penalties is to use actual weight based upon the Commission's 2003 decision. Importantly, hydrocodone will remain on the market in hundreds of formulations as 1) combinations with an array of other agents (including other pain relievers, such as acetaminophen (typically at doses less ≤10 mg) or with antitussive agents [in solid and liquid formulations), 2) single entity products that are extended-release [e.g., Zohydro® ranging from 10 up to 50 mg in a single unit], 3) single entity products with abuse-deterrent features (e.g., Hysingla ER® once daily approved by the FDA in late 2014) and 4) potentially forthcoming immediate-release products. Each of these different formulations will have weights that vary widely based upon the other active ingredients, inactive excipients, and potential abuse deterrent technology agents. Thus, to harmonize penalties, it would appear that considering only weight of the active hydrocodone is the most appropriate approach to avoid proportionality issues in penalties.

Equivalency Issues Related to Potency: Analgesic Equivalency vs. Abuse Liability Evaluations

With regard to severity issues, the proposed amendments define two potentially different recommendations of marijuana equivalency whereby "1 gram of hydrocodone (actual) equates to [4,467]/[6,700] grams of marijuana." The recommendations are derived from two different published sources of analgesic equivalency tables (references contained within the Proposed Amendments to the Sentencing Guidelines): the first which

proposes a 3:2 ratio of hydrocodone to oxycodone (Chicago Department of Palliative Care, a clinical practice guidance) and the second proposes a 1:1 ratio of hydrocodone to oxycodone (Goodman and Gilman, a standard pharmacology text book). Analgesic equivalency tables are used as a general guideline for physicians to employ in the treatment of pain when making determinations regarding the transition of a patient from one opioid to another and to ensure that the pain relief achieved is comparable between the agents. If one examines analgesic equivalency tables from an array of sources, differences in reported relative potency estimates will be found (as was the case here) ranging generally from 1:1, 1:1.5 or 1:2 [oxycodone/hydrocodone]. It is important to recognize that these guidelines are not necessarily derived from empirical studies, are sometimes informed by clinical experience, may include conversions for acute dosing but may also include information from chronic dosing "opioid rotation" observations, are often derived initially from comparisons to morphine (and thus require more than one conversion on relative potency), and are estimates not necessarily derived from validated comparative techniques.

A different approach to understanding equivalency amongst opioid drugs is to focus on their abuse potential and relative potency on abuse-related measures rather than clinical guidelines related to pain-relieving properties. Abuse potential is defined as the ability of any drug with central nervous system activity to produce positive psychoactive effects that may include sedation, euphoria, perceptual and other cognitive distortions, hallucinations and mood changes. These effects are viewed as correlated with or predictive of the risk of abuse and/or addiction. These studies typically are conducted in a controlled laboratory setting where study volunteers are confined as inpatients for the duration of the study to preclude other drug use. In the case of opioid abuse potential studies, the target population for enrollment is individuals with active opioid abuse histories but who are otherwise healthy. These studies administer a broad range of test doses, including supratherapeutic doses, and appropriate control agents (positive and negative if available) for comparison with the test drug of interest. All testing is done under double-blind and typically randomized order conditions. A broad array of outcome measures is collected including physiological (e.g., respiratory, cardiovascular, pupil diameter), subjective

measures (e.g., visual analog questionnaires whereby subjects provide a score using a scale of 0 to 100 for a specific symptom [such as "How high are you?"], street value estimates, observer-rated effects, and cognitive/psychomotor tasks). These studies are required by the Food and Drug Administration (Food and Drug Administration 2010) for new drug approvals for drugs with central nervous system activity and, therefore, this scientific approach is widely accepted for informing federal regulatory decision-making (including Drug Enforcement Agency decisions about where to place agents within the Schedules of Controlled Substances, U.S. Code, Title 21 › Chapter 13 › Subchapter I › Part B › § 812).

Equivalency of Hydrocodone From Abuse Liability Studies

A total of six human abuse liability studies of hydrocodone have been published from 2003 to 2010. Of these, four were conducted in normal healthy non-drug abusing volunteers; this is in conflict with the guidance by the Food and Drug Administration that abuse liability studies for opioids should be done with active opioid abusers. Additionally, each of these examined too few doses to allow for a formal relative potency evaluation using the accepted bioassay method by Finney (Finney 1964) and only one included oxycodone as a comparator.

One study examined directly the effects of oral oxycodone, hydrocodone, and hydromorphone, each tested over a range of therapeutic and supratherapeutic doses, in a cohort of active prescription opioid abusers (Walsh, Nuzzo et al. 2008). For this study, pilot subjects were first tested with the aim of identifying dose ranges that would be roughly comparable amongst the three comparators in order to assess relative abuse liability and relative potency. For subject ratings (such as "drug liking" or estimated street value, which are primary abuse liability outcomes), increased ratings of liking for these drugs were generally evident within about 1/2 to 1 hr after oral administration. The maximum effects were achieved between 1.5 to 2 hours after dosing with a slow decline thereafter. The effects of all three drugs were generally dose-related over the range of doses tested, and the higher doses generally produced a more sustained response. Similar results were found for a broad array of symptoms related to opioid intoxication with no evidence that hydrocodone's psychoactive actions differed in any qualitative way from

those of oxycodone or hydromorphone. In addition, all three drugs acted similarly by producing significant miosis (i.e., a decrease in pupil diameter) and significant respiratory depression (i.e., slowed breathing) in comparison to placebo and did so to comparable magnitudes over this range of test doses. These findings, in part, contributed to the rescheduling of hydrocodone to Schedule II because it was so similar to other Schedule II opioids.

A formal and validated method for comparing the relative potency amongst drugs has been defined as the bioassay for parallel lines by Finney (Finney 1964). This is an accepted and often used test of pharmacological potency in the medical literature.[1] Applying this method to the oral comparison study described, there were numerous dependent measures for which the requisite criteria were met for a valid relative potency assay; thus, these estimates stem from numerous outcomes. The data suggest that the relative potency of these three commonly abused opioids did not differ greatly from one another, which was somewhat surprising based upon previous studies on their relative potencies as analgesics, particularly for hydromorphone. In the published paper (Walsh, Nuzzo et al. 2008), hydromorphone was chosen as the "reference drug" against which the others were compared for relative potency; thus, the Finney assay results for the direct comparison of oxycodone to hydrocodone were not published in that report. However, the statistical analyses were completed for the purposes of presentation on hydrocodone to the Food and Drug Administration during the advisory hearings on upscheduling and approval of Zohydro®. The table below presents those findings:

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[1] From a technical standpoint, this mathematical/statistical test requires that data are collected to achieve a minimum of a three-point parallel line for each dose function (including placebo). Relative potency estimates are determined only if the statistical test (analysis of variance) comparing drug doses confirm the following: linearity, parallelism, no difference in drug preparation, and a significant regression coefficient. Conservative probability levels are employed for the following: linearity $p>.05$, parallelism $p>.05$, drug preparation $p>.05$, and regression $p<.05$.

Table 1: Oxycodone* versus Hydrocodone
*(oxycodone is the reference compound)

Variable	Relative Potency
Subject-rated Measures of Opioid Agonist Effects	
How High do you feel?	0.944
Do you have any Drug Effect?	0.941
Does the drug have Good Effects?	0.928
How much do you Like the drug?	0.976
Skin Itchy	0.921
Nodding	0.936
Dry Mouth	1.016
Carefree	0.899
Agonist Composite Scale	1.004
Fraser Composite Scale	0.953
Observer-rated Measures of Opioid Agonist Signs	
Skin Itchy	0.908
Coasting	0.936
Drunken	0.819
Nodding	0.899
Agonist Composite Scale	0.830
Fraser Composite Scale	0.935
ARCI - Amphetamine	1.054
ARCI - Euphoria	1.025
ARCI - LSD	1.079
Visual Processing	
Flicker/Fusion ` – (min)	0.845
Maddox Wing	0.920
Physiological Response	
Pupils Diameter (min)	0.874
Respiratory Rate (min)	0.731
Overall Mean Relative Potency	**0.929**

Thus, across a broad array of measures, including objective measures such as respiratory rate, subject-rated measures of the drug experience and the observers (who are blind to the study condition) rating signs of opioid intoxication, the mean relative potency

estimate is 0.929 indicating that 0.929 mg of oxycodone will achieve the effects produced approximately equivalent to 1 mg of hydrocodone. Therefore, oral hydrocodone is not equal on a 1:1 basis to oxycodone but it is only slightly less potent.

Using these data, the sentencing guidelines originally based upon the Goodman & Gillman estimates (1:1 ratio) are closest to an accurate representation of hydrocodone's action with respect to abuse potential. Estimates for marijuana equivalency could be derived exactly based upon the relative potency data provided here in relation to the current oxycodone guidelines; these would then differ modestly from either of the current recommendations.

References

Finney, D. J. (1964). Statistical method in biological assay. New York, Hafner.

Food and Drug Administration (2010). Guidance for industry: Assessment of abuse potential of drugs. U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER). Silver Spring, MD.

Walsh, S. L., P. A. Nuzzo, M. R. Lofwall and J. R. Holtman, Jr. (2008). "The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers." Drug Alcohol Depend **98**(3): 191-202.