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Re: Docket No. FDA-2010-D-0026

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The College on Problems of Drug Dependence (CPDD), formerly the Committee on Problems of Drug Dependence, has been in existence since 1929 and is the longest standing group in the United States addressing problems of drug dependence and abuse. College members have reviewed the FDA's draft document, "Guidance for Industry Assessment of Abuse Potential of Drugs" of January 2010, and have several comments that it hopes the FDA will consider. Generally, the College found the FDA's draft document to be a thoughtful and well-constructed document. Our comments are intended to help fulfill the mission of the FDA of minimizing the damage inflicted by drugs with abuse potential and to maximize public health.

Sections I-II. INTRODUCTION & BACKGROUND

1) In the introductory paragraph (**lines 15-24**) it should be communicated to the reader that all NMEs with CNS activity and with an unprecedented mechanism of action require abuse liability assessment. The way this paragraph now reads allows an interpretation for not doing so. To insure that this doesn't occur, the sentence beginning on **line #19** could be modified to read, "Examples of products that are addressed in this guidance include new molecular entities, especially those with an unprecedented mechanism of action, and new dosage forms of drug substances already controlled under the Controlled Substances 21 Act (21 U.S.C. 812(c))." Similarly the sentence beginning on **line #161** should be modified to read, "An assessment of abuse potential may be needed for new drugs, including new molecular entities 162 (NME), and would be required for all drugs with CNS activity that have an unprecedented mechanism of action."

2) General comment with respect to the use of the phrase “mood changes” (p. 1, line 24; p. 4, lines 139-140 and 158, e.g., “*produces psychoactive effects such as sedation, euphoria, and mood changes*”)

Recommendation: The phrase: “...produces psychoactive effects such as sedation, euphoria, and mood changes”

Could be replaced with a more comprehensive phrasing such as:

“...produces psychoactive effects such as sedation, stimulation, perceptual changes/psychotomimetic effects and/or euphoria/mood-elevation”

Rationale: “Mood change” is an ambiguous term that may equally refer to negative changes such as bad mood, mood swings, dysphoria, depression, anxiety, etc., which would not be associated with abuse, but rather avoidance of a drug. Based on historical experience, we can expect psychoactive effects of interest to center around certain domains, including sedation, stimulation, perceptual changes/psychotomimetic effects or euphoria/mood-elevation. Since side effects/adverse events reported during drug development are the primary data source for determining whether a drug shows any “signals” of abuse potential requiring further evaluation, clearly identifying the domains of interest is critical.

Section III. DETERMINING A DRUG'S ABUSE POTENTIAL

3) A. Definitions, p. 4, lines 136-150:

“Abuse potential refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces. These drugs are characterized by their central nervous system (CNS) activity. Examples of the psychoactive effects they produced include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. Drugs with abuse potential often (but not always) produce psychic or physical dependence and may lead to the disorder of addiction.”

The concept of abuse potential encompasses all the properties of a drug, including, for example, chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and diversion history.

Addiction is defined as a chronic, neurobiological disorder with genetic, psychosocial, and environmental aspects, characterized by one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (American Academy of Pain Medicine, American Pain Society, and American Society of Addiction Medicine consensus document, 2001)”

Recommendation: Refer to United Nations Psychotropic Convention and Controlled Substances Act and remove discussion of “addiction”. In addition, the central theme of “continued use despite harm” should be emphasized as the other factors such as craving, compulsive use, etc. are simply collateral phenomena.

Rationale: The references to addiction are not consistent with the Controlled Substances Act nor the United Nations Psychotropic Convention, which refers to

extent or likelihood of abuse, the degree of seriousness of the public health and social problem, and the usefulness as medical therapy. References to “addiction”, which are based primarily on a single point of view (that is, that of the pain medicine field) may simply add confusion.

4) C. What Should Be Included in an Abuse Potential Submission? p. 5, lines 181-197:

“For NMEs, the NDA should include an abuse potential section with the following:

- 1. A summary, interpretation, and discussion of abuse potential data provided in the NDA*
- 2. A proposal and rationale for placing (or not placing) a drug into a particular schedule of the Controlled Substances Act*
- 3. All primary data related to the abuse potential characterization of the drug, organized under the following subheadings:*
 - a. Chemistry*
 - b. Preclinical Pharmacology*
 - c. Animal Behavioral and Dependence Pharmacology*
 - d. Pharmacokinetics/Pharmacodynamics*
 - e. Human Abuse Potential Laboratory Studies*
 - f. Clinical Trial Data Relative to Abuse and Dependence Potential*
 - g. Integrated Summaries of Safety and Efficacy*
 - h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing and Labeling)”*

Recommendation: In particular with respect to point “1. A summary, interpretation, and discussion of abuse potential data provided in the NDA”, it is recommended to make reference to the 8 factors defined in the Controlled Substances Act.

Rationale: Although it may be the mandate of the Secretary of HHS to consider the 8 factors, it is a useful framework to help sponsors understand and interpret their own data, given that they, like the HHS, must make conclusions regarding the appropriate schedule for the drug based on the 8 considerations outlined in the Controlled Substances Act.

5) C. What Should Be Included in an Abuse Potential Submission? p.5, line 193 and p. 12, line 498 (Heading)

“Human [Abuse Potential] Laboratory Studies”

Recommendation: It is recommended to use the word “clinical” rather than “laboratory” to describe human abuse potential studies.

Rationale: These studies are not performed in a laboratory and use of the phrase “laboratory study” implies less rigor than would typically be afforded a phase 1-type clinical pharmacology study, performed for registration purposes.

Section IV. APPROACHES AND METHODS FOR ABUSE POTENTIAL ASSESSMENTS

- 6) The ease of synthesis of a drug can be a determinant of its abuse liability. The sentence beginning on line #293 could be modified to read, "Information on extractability and solubility of a drug, as well as its ease of synthesis, is relevant to the drug’s abuse potential and should**

be addressed.

7) Drug-containing products can be combusted and the drug inhaled as smoke. Many CNS-active compounds are bioavailable via this route. To include this possibility, the sentence beginning on **line #316** could be modified in the following way, "Additional experimental variables may include exposure times to the solvent, agitation, varying the surface area (such as from intact to being ground, crushed, or cut up into pieces), combustion releasing the drug into smoke, and ease of crushing tablets or destroying the dosage form matrix."

8) Although the abbreviation, "API" (e.g., **line #338**), is defined within the text, it should also be included in the list of abbreviations on p. 20.

9) **p. 8, lines 340-342:**

"A new formulation that is designed with a possible claim of abuse deterrent qualities should be studied for relative abuse potential in human pharmacology studies. The abuse potential of the new formulation should be compared to a previously approved product that serves as a positive control."

Recommendation:

Provide more information regarding the methodology of clinical studies to evaluate abuse-deterrent formulations. If detailed explanations are beyond the scope of the document, there are useful references that could be provided (such as articles derived from CPDD and other special symposia [e.g., Katz et al., 2007; Drug and Alcohol Dependence special issue Drug Alcohol Depend 2006; 83 Suppl 1]).

In addition, it is recommended to state more clearly that these assessments of abuse potential should be based on the standard abuse potential design discussed in later sections. This is implied by the above wording, but "human pharmacology studies" could still be misinterpreted to mean pharmacokinetics studies.

Rationale: It is agreed that studying the abuse potential of abuse-deterrent formulations in human clinical studies is critical to the pre-market risk evaluation of these products. However, it may be helpful to further describe the nature of these studies as it is a source of confusion for many sponsors (for example, do these studies involve different routes of administration? Different forms of tampered and/or intact product?) or alternatively articles on this subject can be referenced for more detailed discussions. In addition, a clearer explanation of these studies will reduce the potential for misinterpretation that pharmacokinetic studies would be adequate. While understanding the pharmacokinetics of the formulations is useful, it is not sufficient for understanding the relative abuse potential and special risks of the different products, as abuse-related effects may not always closely follow plasma concentrations.

10) **Lines #369-#372** describes the routes of administration to be used in preclinical studies. One objective of preclinical studies is to evaluate the test compound using routes of administration most likely maximizing the likelihood for abuse. Typically, this means using routes that maximize the speed of effect. For several kinds of studies, such as drug self-administration studies, this pragmatically means delivering the drug intravenously. This paragraph needs to be strengthened to insure that testing maximizes the likelihood for inducing abuse-related effects. A sentence could be added to the end of this paragraph

reading something along the lines of the following: "These additional routes should include routes of administration maximizing the speed of effect where feasible, for instance, the intravenous route should be used in tests of drug reward."

- 11) Lines 374-380** discuss the importance of determining plasma levels of the parent drug and its metabolites in preclinical studies and relating them to clinical plasma levels. Caution should be exercised when applying the importance of plasma levels in these sorts of studies. Different species can have different densities of receptors that are sensitive to test drugs that can alter the relationship between plasma level and pharmacodynamic effect. What defines a preclinical study that has been thoroughly conducted is less that clinical-like plasma levels had been obtained, and more that a complete dose-effect curve was evaluated to include obviously behaviorally-active doses.
- 12)** The spirit of the sentence beginning on **line #396** was interpreted to mean that doses up to those that are maximally tolerable should be tested in preclinical studies so as not to omit testing those that may have abuse-related effects. This is an important point to make. The phrase ending that sentence, "or indicate that further investigation is appropriate," is unclear. It is suggested that this sentence be broken into two sentences to read, "Information resulting from adverse effects or other safety concerns should be used to set dose level limits. Doses should be tested to included those that are maximally tolerable to insure that an adequate dose range has been evaluated."
- 13)** A concern is that too much emphasis is given to conditioned place preference testing, especially considering that this procedure is not as well validated as other procedures (e.g., drug self-administration), and that experts sometimes disagree regarding the interpretation of such tests (**lines 410-424**). For instance, conditioned place preference procedures are thought to involve classical (Pavlovian) conditioning in which the environment associated with drug administration is established as a conditional stimulus. Although it is often concluded that when the subject spends more time in the drug-paired environment during testing it is showing a positive attraction to drug-like effects, there is a substantial literature documenting that conditional stimuli based upon abused drugs can actually come to elicit effects opposite to those the drug upon which they are established elicit (for reviews see, Siegel, 1991 and Siegel, S., et al., 2000). This often overlooked possibility can misdirect conclusions to the opposite of what they should be.
- 14)** The words, "related to self-administration", on **line #410** needs to be deleted when discussing conditioned place preference studies. Never in the history of the subject in conditioned place preference studies does it emit any behavior that results in drug delivery, which is the hallmark of drug self-administration studies, and which makes these two procedures unrelated.
- 15)** The paragraph that extends from **line #416 to line #424** should be re-written to refer to either self-administration or conditioned place preference, and not to include those jointly as if all drug relationships observed under self-administration are also always observed under conditioned place preference, and vice versa. For instance, the NMDA antagonists are identified as being false negatives, but abused NMDA antagonists such as phencyclidine and ketamine are self-administered by the non-human primate (e.g., Moreton et al., 1977; Pickens et al., 1973).
- 16)** In the paragraphs extending from **line #436 to line #453** describing tolerance and dependence testing we have the following suggestions: First, these are the only paragraphs

within this section entitled, "C. Animal Behavioral Pharmacology Studies," that mixes testing in laboratory animals and testing in humans and this can lead to confusion. For example, it is ethically questionable to administer maximally tolerable doses to human subjects for extended periods of time in order to ultimately determine if withdrawal effects emerge upon drug discontinuation, as one might do in a thorough, laboratory animal study. We suggest that these paragraphs be re-written to focus exclusively on animal testing. Second, on **line #446** the words, "to avoid symptoms of *withdrawal* or "bad feelings", should be changed to, "to prevent signs of withdrawal including those of apparent malaise." Laboratory animals can't report "symptoms" or "bad feelings". Thirdly, the sentence beginning on **line #448**, "Correlation of results with plasma...", should be deleted. Therapeutic plasma concentrations may be irrelevant to a drug abuser who may obtain supra-therapeutically relevant plasma levels and consequentially, physical dependence.

17) The section entitled, "D. Application of Good Laboratory Practice (GLP)", **lines #468 to #474**, is in error, at least historically, and if left to stand, could very well compromise a thorough and the most professional assessment of the abuse potential of drugs. Historically, the FDA has not required abuse liability procedures to be conducted under GLP. A reason why GLP was not required for these studies has likely been to insure scientific flexibility under conditions in which procedures are still evolving, and as a consequence, to maximize the thoroughness in which abuse liability assessments are made. Additionally, the foremost leaders who have developed the key procedures currently used for abuse liability assessment are academicians, and do not work in CROs. Imposing the regulatory morass of GLP upon academicians who don't have the infrastructure to do so will prevent many from continuing to conduct abuse liability assessments, and frankly, the evolution of these procedures will be stifled. It is also unclear how GLP regulations can be imposed upon abuse liability assessment procedures for these have, here-to-fore, been considered as part of the "pharmacology" of a compound, and other pharmacology tests are not required to be conducted under GLP.

An additional problem with this section is its reference to ICH S7A which it uses to support the need to apply GLP requirements to abuse liability tests. ICH S7A, however, describes CNS core studies as GLP-compliant and additional targeted studies as GLP-compliant when feasible. Likewise, in order for the present guidance document to ensure consistency with ICH S7A, the text in this section should indicate that abuse potential studies should be GLP compliant to the extent feasible. Additionally, abuse liability studies should be considered within the special safety pharmacology studies for which the ICH S7A suspends GLP requirements (Section 2.11): "Due to the unique design of, and practical considerations for, some safety pharmacology studies, it may not be feasible to conduct these in compliance with GLP."

Section V. HUMAN LABORATORY STUDIES

18) Section V. A. Human Abuse Potential Study in Recreational Drug Users

General Comments:

Overall this section is very well-written and consistent with existing guidelines and best practices. We were pleased to see that double blind, double dummy, placebo, and positive comparator controlled, crossover designs were recommended, and that treatments should include placebo and multiple doses of the investigational drug and positive control. The dose ranges suggested for evaluation are generally appropriate and the recommendation to evaluate dose-response is an important factor that is often overlooked. We were pleased to see that

inpatient studies were recommended and that appropriate safety monitoring should be implemented, as serious or severe side effects are possible when evaluating higher doses that may have been previously studied in only a small sample of subjects. There are a few areas however, where expansion or clarification may be needed.

General Recommendation:

It is recommended to reference the ICH GCP guidance for human abuse potential studies, rather than a pre-GCP FDA guidance, which may no longer contain the most relevant and up-to-date information.

Rationale: Since these studies are intended to support a marketing application, it is recommended that ICH GCP guidance be referenced.

19) Section V. A. Human Abuse Potential Study in Recreational Drug Users, 1. Subjects

There is some inconsistency with respect to descriptions of the subject population, both in this section and in other sections where subjects are mentioned. Specifically:

p. 13, line 533-534:

“Screening for substance abuse during the study is often necessary to ensure that subjects are not currently abusing other substances.”

Recommendation: It is recommended that positive urine drug screen (and breath alcohol) results be documented prior to dosing and subjects rescheduled as necessary, rather than excluding subjects who test positive.

Rationale: It is agreed that subjects should be screened for drugs of abuse; however, if subjects are expected to be “current or recent recreational users”, it is likely that they will be using drugs recreationally and may test positive on drugs of abuse screens. While co-administering study drugs and recreational drugs should be avoided for safety and data integrity reasons, removing or excluding such subjects from the study contradicts the main inclusion criterion that requires these subjects to be drug users.

20) p. 13, line 535-536:

“Exclusion criteria should include a current diagnosis of substance dependence, current abuse, and current treatment for a substance-related disorder”

Recommendation: Excluding subjects with dependence or substance abuse treatment history is appropriate; however, it is not recommended to specifically exclude subjects with a diagnosis of “abuse”, since it is contradictory to the main inclusion criterion.

Rationale: While it’s agreed that dependent individuals and those who have received substance abuse treatment (as an indicator of “dependence”) should not routinely be used in these studies for ethical and physiologic reasons; excluding subjects with a diagnosis of “abuse” is contradictory. The words “abuse”, “drugs abused”, “duration of abuse” and “abuser” are used frequently in preceding and later sections of the guidance, so it’s unclear how a subject can be a recreational drug user who currently uses drugs, but does not meet substance abuse criteria. This would significantly diminish the available population and may have an impact on scientific integrity as it would result in only the very lightest users being studied (i.e., most current recreational users are likely to meet as

least some criteria for abuse, as defined by standard, non-quantitative assessments like the DSM-IV). Very light users may not tolerate higher doses well and may be more likely to give a false negative response (as can be observed in non-drug users).

21) p. 13, lines 538-543:

“Recently, some abuse potential studies have also been conducted in drug naïve healthy subjects and this is an area of needed research. These two populations may differ in important ways, including in their ability to identify subtle differences in drug effects that are relevant to abuse assessment.”

“For the study to be interpretable, the subjects should be able to reliably report “drug-liking” and be able to provide ratings of drug experiences related to the drug’s subjective effects and similarity to specific classes of known drugs of abuse.”

Recommendation: It is recommended to clarify the regulatory need to examine responses in healthy drug-naïve subjects. Furthermore, it is recommended that a sentence be added after **line 541** that reads, “Research to date would suggest that either positive or negative results obtained from drug naïve healthy subjects would be difficult to interpret without other studies completed in drug-experienced subjects. Finally, it is recommended that we change **line 543**, to read “For any study...” to insure that the document is not refereeing to drug-naive healthy subject studies.

Rationale: It’s unclear whether this paragraph is suggesting abuse potential studies should be conducted in healthy volunteers, in addition to recreational drug users; however, studies in healthy subjects have a number of limitations, the most serious of which is the higher risk of false negative results (Griffiths et al., 2003). Although it may be interesting from an academic point of view to examine differences between these populations, from a regulatory standpoint, it’s unclear what additional information such studies would provide, as an adult drug-naïve individual is not at high risk for abusing these drugs once on the market. The populations at highest risk for abusing these prescription drugs are the recreational drug users/abusers and dependent individuals, while potential risks to the patient population (the other group of individuals most likely to be exposed to the drug), are probably best estimated using spontaneous reporting of adverse events, cases of misuse/diversion, or simple mood or subjective scales (as described in a later section).

22) Also p. 14, line 550-553:

“Other factors that influence the significance of study results include demographic range with respect to age, sex, and race, drug of choice, frequency of participation in drug abuse studies, duration of drug abuse, variety of drugs used, and duration of drug abstinence.”

Recommendation: Clarify how these factors are used by the agency in the analysis or interpretation of study data.

Rationale: It’s not clear whether the sentence indicates that these factors should simply be recorded or whether the agency will view some study results as more or less “significant” depending on these factors. While these factors may result in subtle differences in response, the significance (validity) of the study is

determined by the appropriate response to the internal positive comparator. The use of an internal positive comparator in every study ensures that the data remain interpretable, despite potential differences in population make-up or methodology between different clinical sites.

23) Section 2, p. 14, lines 555-584

“The human abuse study measures repeated single-dose administrations over a period of time, determined by the time course of the drug’s effect.”

Recommendation: It is recommended that the second sentence on **line 558-559** be changed to read, “Most human abuse studies utilize within-subject Latin Square cross-over designs to measure the effect of different doses of drug administered acutely and/or sequentially to determine the time course of the drug’s effects.” It is also recommended the following sentence be added at the end of this section or about **line 585**, “Alternative designs involving repeated dose administration, drug interaction studies, or drug reinforced self-administration measures may be considered valuable and sometimes necessary on a case by case basis.”

Rationale: The design section proscribes an acute dose Latin Square design which is very common and probably recommended in most cases, but should not be considered the only possible design.

24) Section 3, p. 14, lines 591.

“Therefore, it is recommended that subjects stay overnight following administration of each dosage.”

Recommendation: It is recommended that the word “preceding” be inserted between “overnight” and “following” to read, “Therefore, it is recommended that subjects stay overnight preceding and following administration of each dosage.”

Rationale: This change will account for a wash-out period

25) Section 6. Analysis of Data, p. 16, lines 642-651:

“If the study consists of a heterogeneous population of identifiably unique groups, analyses of the data subsets corresponding to each group should be conducted. For example, a population of recreational users of central nervous system depressants could include individuals who prefer to abuse sedative-hypnotic drugs over alcohol. In a study evaluating a new central nervous system stimulant, the study population could include individuals identified as cocaine abusers, for example. These individuals are often polydrug abusers and may prefer to abuse drugs from other pharmacological classes. The differences in preference of each population group to the drug class could yield different results. Further research in this area of analysis would help determine under what circumstances these subgroup analyses can be performed and are useful.”

Recommendation: Stratification by subject “preference” is not recommended, as preference is very difficult to reliably quantify. In addition, a polydrug using population may be preferable in some situations, such as for studies of novel CNS drugs.

Rationale: It may be difficult for subjects to reliably report their “favorite” drug, as many subjects use a variety of drugs, and preference is likely to be highly

situation or context dependent. In a medical/clinical setting such as that of an abuse potential study, preference is likely to have little meaning as it isn't consistent with a typical drug-taking situation. If a subject is pre-screened for their liking of the class of interest, assessing and stratifying by "preference" may not provide any additional benefit. In addition, although subjects may report a "preference" for a particular positive comparator drug, it doesn't necessarily lead to a greater probability of observing a true positive result with the investigational drug, as many CNS drugs in development are subjectively or pharmacologically unlike existing drugs of abuse. In such cases, the use of polydrug-using subjects, who use a variety of different compounds, is probably preferred to a "specialist" as their ratings of novel drug effects can be considered more reliable.

26) Section 2. Design, p.14, lines 572-573:

"The assessment of abuse potential can include co-primary endpoints and some secondary endpoints of interest, if appropriate. However, no more than three primary measures should be recommended"

Recommendation: Although selecting primary endpoint(s) can serve practical purposes such as calculating study power, defining study validity or selecting "responders" during pre-study qualification, it is recommended to clearly state that conclusions regarding abuse potential are based on all data and variables.

Rationale: Because drug abuse is complex and multifactorial, abuse potential studies have traditionally been considered 'pharmacologic' studies. Suggesting the use of a primary and secondary endpoint approach is more appropriate for an efficacy evaluation, where a single-direction, binary (treatment effect vs. no treatment effect) response is expected. At this stage of research in the field, it is probably not warranted to recommend the use of a primary endpoint approach (other than perhaps for the practical purposes mentioned above). If it is not clearly stated that all data are considered in the evaluations/conclusions, sponsors may misinterpret the discussion of primary endpoints to mean that they can base their conclusions only on these endpoint(s), as would be typical for a confirmatory efficacy trial. This could result in misleading or false conclusions regarding the abuse potential of the drug, if the secondary endpoints do show significant effects. In addition, the rationale for having no more than three primary measures is unclear. Is this number based on a specific statistical consideration?

27) p.14, line 575-579:

"Although the use of 12 to 25 subjects has been seen in past studies, in some recent studies as many as 40 subjects have been used. We don't recommend a specific number of subjects for a study; the study should be sufficiently powered such that we can determine the statistically significant relationship of the test drug to placebo and positive control to the primary and secondary outcome measures"

Recommendation: Clarify the discussion of study power. Specifically, the need to power for all primary and secondary endpoints and all contrasts may not be practical given the large number of calculations needed. As stated earlier, while primary endpoints should not be considered in the traditional confirmatory trial sense, it can be useful to designate one or two endpoints simply for the purpose of calculating power. An alternative approach is to power the study to detect a

minimal difference regardless of the contrast in question, for example, using existing comparator data to estimate the variance.

Rationale: Practically, these studies typically include a relatively large number of measures, endpoints, and contrasts. For a relatively simple study with 20 measures each with 2 or 3 endpoints, 5 treatments arms, and 10 contrasts, one would need 600 individual sample size calculations. Therefore, determining the power based on all contrasts (test drug to placebo and positive control), and primary and secondary endpoints, may not be practical. In addition, data on abuse potential measures are not normally available for the investigational drug prior to the study. Even if available, using data from previous studies with the investigational drug may not be useful if the methodology (i.e., ascending dose vs. crossover) or subject populations (e.g., healthy volunteers vs. recreational drug users) are significantly different, as this can lead to the use of inaccurate variance estimates in the sample size calculation.

28) p.14, line 583-584:

“The washout period of a crossover designed study should be at least five times the maximum half-life of the longest acting drug in the study”

Recommendation: Include a discussion of alternative study designs for long half-life drugs. The absence of such discussion may lead to inappropriate design decisions, such as the use of a parallel group design.

Rationale: While we agree that 5-times the longest half-life is an appropriate guideline for a crossover study, a full pharmacokinetic washout may not be possible in all situations. For many drugs such as cannabinoids and benzodiazepines, subjective effects may not persist beyond 12 to 24 hours, despite residual plasma levels, and therefore a full pharmacokinetic washout may not be needed in all cases. In addition, for very long half-life drugs (>100 hours), alternative designs may be needed, as a full washout would not be feasible and would place an undue burden on the subjects. The absence of some discussion of alternative designs may lead to inappropriate design decisions, such as the use of a parallel group design. (For example, other clinical regulatory guidance such as the ICH E14 guidance for thorough ECG studies, do recommend a parallel design for long half-life drugs. However, given the subjective nature of the assessments, simple parallel designs would not be appropriate for an abuse potential study). The existing Health Canada Guidance document (2007) and several review articles do suggest possible alternatives (McColl & Sellers, 2003; Chen & Tsong, 2007), and these documents could potentially be referenced in place of a detailed description.

29) Section 4. Selection of Doses and Controls

General Recommendation: Include a discussion of negative controls in human abuse potential studies.

Rationale: Unlike in the animal behavioral section of the draft guidance, there is no mention of the use of negative controls in human abuse potential studies. Given that there are no established guidelines for “clinically-important” differences on abuse potential measures, negative control data can be highly

relevant for distinguishing expectancy and minimally detectable effects from relevant abuse-related effects. The use of negative controls (and/or or more than one positive control) may in some cases even be critical to ensuring valid abuse potential conclusions and proper scheduling placement.

30) p. 15, line 604:

“The positive control should be a drug of abuse in the same pharmacological class as the test drug”

Recommendation: Discuss alternatives for selecting a positive control drug when the investigational drug has a novel mechanism of action. For situations where the investigational drug has a novel pharmacology, it is recommended to select the positive control drug based on the investigational drug’s side effect and behavioral profile, rather than simply the indication.

Rationale: While existing abuse potential study guidelines recommend using a positive control of the same pharmacologic class as the investigational drug, this doesn’t fully acknowledge the reality that a large proportion of CNS drugs in development have novel mechanisms of action that do not fall into existing pharmacologic classes associated with abuse. Since selecting a positive control drug in such situations is not as straightforward, it might be helpful to provide additional advice. For example, examining adverse events or behavioral effects from preclinical and early clinical development can suggest an appropriate control(s).

31) p. 15, line 605-606:

“Additional useful information can be obtained if the positive control has the same medical indication as the test drug”.

Recommendation: Clarify the scientific rationale for the positive control and investigational drug having the same medical indication.

Rationale: The relevance of therapeutic indication to abuse potential is unclear, as abuse potential is primarily related to a drug’s subjective (psychoactive) and reinforcing effects. These effects can be best estimated based on the drug’s side effect and behavioral profile, while a drug approved for the same indication may not necessarily have subjective or psychoactive properties in common with the investigational drug. Further, for some indications, there are no controlled substances that could be selected as a positive control (for example, depression, psychosis, neurodegenerative diseases, etc).

32) Outcome Measurements, p. 15, lines 618-638:

Overall, the discussion of outcome measures is appropriate and it’s agreed that ratings of liking and disposition to take the drug again are highly relevant; however, there are a few items that are in conflict with existing abuse potential recommendations (e.g., Griffiths et al., 2003).

Recommendation 1: Discuss the use of behavioral assessments, such as drug-versus-money choice procedures, as measures being most directly related to the likelihood of abuse.

Rationale: Behavioral choice assessments, such as money-vs-choice procedures and adaptations thereof are not mentioned in the guidance. This

omission is puzzling, given that these measures are the closest approximation we have for assessing reinforcement in humans, without conducting a separate self-administration study.

Recommendation 2: Do not recommend listing drug identification/similarity questionnaires as “primary” variables.

Rationale: Drug identification questionnaires, while useful, are not considered direct measures of abuse potential and interpretation can be difficult. This is especially true for novel drugs, which may not be identified clearly as being similar to existing drug of abuse, but may nonetheless have significant abuse potential. Further, because these measures can only be administered to subjects who have actually experienced the drugs in question, the differences in sample sizes for the different drug class scales can complicate the statistical analysis and limit the conclusions that can be formed based on these scales, especially where the sample sizes are very small.

Recommendation 3: It is recommended to avoid ambiguous terms like “high” and “spacey”, and refer simply to drug liking, willingness to take the drug again, and other subjective effects.

Rationale: While terms such as “high” and “spacey” have historically been included as scales in many studies, they are typically associated with a high degree of variation and ambiguity in the results. This is likely due to the ambiguous nature of these terms, as they can be interpreted by each subject differently.

33) p. 16, line 677-679:

“Similarly, cognitive tests that assess whether memory, perception, attention, language ability or consciousness are altered by a drug can indicate the presence of certain effects that drug abusers might find desirable”

Recommendation: Clarify the interpretation of cognitive and other drug effect data in the evaluation of abuse potential, and discuss the implications of these data with respect to safety and public health risk.

Rationale: While changes in perception may be desirable to some users, it’s unclear how impairments in memory, attention or language ability would be desirable, unless this refers to enhancement of such effects. In this case, it’s not an issue of recreational abuse, but rather misuse for the purposes of performance enhancement (e.g., studying, staying awake during night driving, etc). In addition, an important reason for evaluating cognitive impairment is to determine the risk of negative outcomes to the potential abuser in order to understand the potential public health risk of the drug.

34) C. Clinical Trial Data Relative to Abuse Potential Assessments

General Recommendation: Discuss the limitations of adverse event data for making conclusions of abuse potential. In addition, it is recommended to clarify how these data are used by the agency in their evaluations, so that sponsors can make appropriate decisions and conclusions regarding their products.

Rationale: While adverse events can be useful for identifying which drugs may require further abuse potential evaluation (and for guiding the design of such studies), the limitations of these data are not addressed in the guidance. The primary limitations are that the magnitude and relevance of spontaneously reported events to abuse risk has not been determined and there are so far no data in the literature to support a direct correlation between these events and actual abuse (or even prospective subjective measures used in human abuse potential studies). Some clarification of how these events contribute to the agency's final conclusions regarding the drug's abuse potential will help sponsors to make appropriate decisions.

35) p. 17, line 689-690:

"...safety data for mood elevation, sedation and psychotomimetic effects can provide useful information"

Recommendation: Include "stimulant" effects in the above sentence.

Rationale: For some drugs, stimulant effects would be of interest to abuse potential. Stimulant-like effects, such as those related to alertness and attention, may be important to understand, even in the absence of concurrent euphoric effects.

36) p.17, line 698-700:

"Various quantitative measurements will be useful in providing objective data to assess dependence"

Recommendation: It is recommended that the guidance acknowledge that existing dependence checklists designed and validated for specific drug classes may not be appropriate for use with novel drugs.

Rationale: While existing scales may be useful for certain classes, some of these class-specific scales may not be appropriate for novel drug classes, where the profile of discontinuation effects may be different. If careful monitoring of discontinuation events began early in clinical development, it may be possible to use this information to design a specific checklist (or modify an existing checklist) for use in later stage trials.

37) p. 17, lines 715-719:

"2. Provide complete information, including case report forms and final outcomes, on all instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study."

Recommendation: Clarify the rationale for providing full case reports and outcomes for all situations identified in the above statement, in particular for those which are very unlikely to have any relationship to abuse. Training monitors and site staff to be aware of the potential for diversion, misuse and abuse and to encourage careful documentation of these suspected cases would provide more useful and concise information for estimating diversion risk.

Rationale: While it's agreed that cases of addiction, abuse, misuse, overdose, drug diversion and drug loss are potentially important indicators of abuse risk, it is unclear how cases of protocol deviations, acts of non-compliance, losses to follow-up, drop-outs and lack of efficacy are relevant to abuse risk, when the vast majority of such incidents will have no relationship whatsoever to abuse or dependence. In a typical drug development program, which may include thousands of patients and hundreds of such reports, providing case reports of all such events would not be practical and may result in large volumes of essentially uninterpretable data.

Section VI. Postmarketing Experience

It is clear that this section is only there for guidance about obtaining information on abuse that might be available after an NDA is submitted in the U.S. There is little discussion or reference to the draft Guidance on REMS recently published by the FDA. This section would benefit from cross referencing that document and placing these recommendations in this broader context.

38) Paragraph 1:

This paragraph pertains to the situation where a drug is first made available outside the U.S. and then is submitted for approval for the U.S. In addition to obtaining adverse event information and the other information referred to in this paragraph, other sources of information on potential foreign abuse can be obtained from such sources as a) a thorough scientific literature review, b) a search of internet sites that may describe abuse, c) a complete analysis of any control provisions associated with use of the drug in countries where it is available. Data from other countries, if available, would be essential in making a determination regarding abuse potential of a drug in the U.S.

39) Paragraph 2:

This paragraph pertains to the situation where an already marketed drug in the US is reformulated. It does not make clear if the reformulation was done to deter abuse, or for other reasons. In those cases where the reformulation is to an abuse deterrent form, the importance about providing all information about the currently available formulations is much greater than when the reformulation is for another reason.

Although search of the listed national databases for information about abuse of the medication is good advice, perhaps this section should point out some of the limitations of obtaining brand-specific information from these types of sources? Most national databases do collect some data on brand specific formulation but do not release these data. In addition, there are no published peer-reviewed standards for identifying and validating the attribution of formulations in the major federal data collection systems; for example there is no national standard for attribution of causality in poisoning deaths among medical examiners. When such data are collected, there are significant limitations to the data that greatly limit their usefulness. Additionally, the data from these national databases are often reported years after the data are collected and do not contain information regarding geographic specificity. This type of information is critical to address problems quickly before they may spread. The FDA is aware of this and point out this issue in the last sentence, but offer no guidance in how to address these issues.

The Guidance states that data sources other than federally funded databases are anecdotal. This represents a lack of understanding of the both the federal databases and proprietary databases. The proprietary databases provide drug specificity of both formulation and brand along with geographic specificity and timeliness. The lack of recognition of the value of these data sources is a major concern. Sources that provide more detailed and better information than the federal databases include the RADARS[®] System run by the Denver Health Authority and NAVIPPRO[®] run by Inflexxion.

40) Paragraph 3:

Any good assessment of the abuse liability of a drug must include information on market penetration. This provides a rate that permits comparison with other products on the market. Denominators can include number of prescriptions, amount of drug produced, unique recipients of dispensed drug or population based rates. In many cases, more than one denominator should be used.

With a low penetration drug, many potential drug abusers may not have had the opportunity to abuse the drug. Low post-marketing observed abuse rates in such a situation may not reflect a specific abuse-deterrent quality of the new formulation being evaluated, but rather a lack of opportunity for abusing the drug that is a function of the social setting in which all drugs are abused. While denominators are important, inclusion of dispensed availability in statistical models runs the risk of overadjusting and removing actual variations between products. Therefore, when multiple denominators of dispensing-based data are to be considered in statistical modeling, there should be an effort to understand and document whether pharmacy-based data reflect street level availability.

41) Paragraph 4:

In addition to quantitative data, qualitative data can provide important and timely information on the abuse liability of a marketed drug. Sources of the information include surveys, focus groups, ethnographic studies, media monitoring, literature reviews and Internet searches. These data are essential to provide context to any quantitative data.

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