PhRMA-FDA Dialogue Session
Abuse Potential Assessments

February 20, 2008
Bethesda North Marriott

Panel Responses & Discussion

The opinions and information in this presentation are those of the authors and do not necessarily reflect the views and policies of the FDA

CSS-PhRMA Dialogue Session

- Planning & discussions with PhRMA over the past couple of years
- Focus of this meeting relates to the prospective study of abuse potential
- Numerous such discussions on abuse potential assessments have been held by a variety of groups over the past 20 years
- Provides a forum for discussion of many of these issues
- Emphasizing the Agency's approach to drug scheduling, that includes:
  - Data needs
  - Evaluation of data
  - Decision making

Controlled Substance Staff

- Serves as the CDER and FDA focal point for all activities regarding drug abuse and dependence and drug scheduling for the Department HHS:
  - Policies in drug scheduling, legislative & regulatory initiatives.
  - Risk management consultation on drugs of abuse.
  - Reviews & responds to citizen petitions.
  - Consultant to OND Review Divisions on abuse potential reviews for INDs & NDAs of CNS-active drugs.
  - Reviews & advises Industry on developing preclinical and clinical protocols for assessing abuse potential of new drugs.
  - Identifies new trends and risks related to drug abuse.
  - Advises DEA on estimates of medical need in their determination of manufacturing quotas for Schedule I & II drugs and the DEA licensure of Schedule I drug researchers.

CSS-PhRMA Dialogue Session

- Focus on Interdisciplinary Drug Review
  - Preclinical studies
  - Clinical studies
  - Assimilation of and interpretation of data
- Does not focus on
  - Assessment of abuse post marketing.
  - Surveillance, monitoring and interventions methodology.
  - Roles of other Agencies in the drug scheduling process.

CSS-PhRMA Dialogue Session

- Four Fictitious Drugs Under Development (Cases) are the subject of the discussion
- A series of questions relating to development and assessment of the drug's abuse potential and Agency's perspective have been put forward by PhRMA
  - Throughout we have added a series of comments on various issues related to the fictitious data for each fictitious drug
  - Our comments rely on general principles and approaches.
  - No comments made during these discussions apply directly to current or future applications.
  - Because of time limitations, no drug case presented will have complete data and the assumption is made that all assays and studies for which data are provided were performed correctly.

Frequent Questions

- When in the drug development process is the earliest time that the Company can know that its drug will not be scheduled and does not have abuse potential?
- For novel mechanisms of action, how much data is necessary to establish “no abuse potential”?
- For unique members of a drug class that is recognized historically to have abuse potential or to lack abuse potential, what is the minimum required (necessary) abuse potential data to determine if a drug is to be scheduled if there is general agreement that the drug should be scheduled?
- What is the Agency’s perspective on different abuse potential for drugs with different indications?
- What is the burden of evidence necessary to substantiate that a new unique product is different from predecessor drugs that are scheduled and should be considered for a different schedule?
- What amount of data is necessary to confirm that a new drug in a class that is not scheduled does not have abuse potential?

FDCA: Content and Format of an NDA
21 CFR §314.50 Subpart B

(*vii*) If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the CSA…*must be included in the NDA*. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

CSA (21 U.S.C. 812 (b)): HHS Scheduling Recommendation to DEA

Three Findings are Required:

(A) Potential for abuse

(B) Currently accepted medical use in treatment in the United States.

(C) Psychological or physical dependence.

CSA (21 U.S.C. 811 (b)): HHS prepares a scientific and medical evaluation of the drug and considers 8 factors determinative of scheduling

Eight factors:

1. The drug's actual or relative potential for abuse
2. Scientific evidence of the drug's pharmacological effects, if known
3. The state of current scientific knowledge regarding the drug or substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence potential
8. Whether the substance is an immediate precursor of a substance already controlled.

CSA: “Abuse" is described in the legislative history

- Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.
- There is significant diversion of the drug or substance from legitimate drug channels.
- Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substance.
- The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

[Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.]

Public Health Concerns

- *Prescription drug abuse* is a nationally recognized issue, that is discussed in the news media and other public fora
- Risk management and risk communication are often needed, in addition to the regulations that result from CSA scheduling
- The abuse potential studies do not always address the manner in which a drug is abused
- New routes of administration and new formulations of already scheduled drugs introduce new safety/abuse risks and may increase the abuse potential of a drug

CSS Panel

- Michael Klein, Ph.D. Director (acting)
- Silvia Calderon, Ph.D., Pharmacology & Medicinal Chemistry, Team Leader
  - Use of MedDRA Terminology in Assessing Abuse Potential
- Katherine Bonson, Ph.D. Pharmacologist
  - Drug Discrimination Paradigm
  - Self Administration Paradigm

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  notably Mark Ammann, Pharm.D.
- Alan Goldhammer, Ph.D.,

  Deputy Vice President, Science - Regulatory Affairs, PhRMA

Sample Case A

Novel mechanism for an indication for Female Sexual Dysfunction where scheduling is not commercially viable

What package is needed to substantiate that this product does not have abuse potential?

Pharmacology & Pharmacokinetics

Comments on Slide 7:

- Binding data identify direct drug interactions with CNS receptors.
- Active metabolites in humans need a full binding assessment and PK profile

- Ki of 350 nM at D2 receptor cannot be interpreted until the therapeutic dose, plasma concentration and brain penetration of the drug are known.
- If the therapeutic dose is very high, it may produce sufficient plasma concentrations to activate D2 receptors, which can impact abuse potential.

- "Receptor X agonist": Conclusions about abuse potential cannot be made without full information on the purported mechanism of action – even if it's a novel receptor.

- Distribution in nucleus accumbens and striatum suggests that drug may produce dopaminergic effects in reward areas
- The increase in DA seen only in the PFC with microdialysis may be because autoreceptors there may allow for a measurable signal. In other regions, it is harder to get a measurable signal, even if the DA increase is functionally significant.

Q1: From the preclinical data provided, what, if any, concerns would be raised on the possible abuse potential of FSD-204?

Q2: Is any further preclinical data required for interpretation?

- CSS evaluation of the preclinical data requires full protocols (not summaries) for each study conducted, plus individual and mean data from each study:
  -- Receptor binding for parent compound and active metabolites
  -- Studies that determine agonist vs. antagonist activity
  -- Second messenger system or other functional studies
  -- Functional Observation Battery:
    * Observation duration should be at least 10-15 min for a comprehensive understanding of behavioral changes resulting from drug administration or discontinuation.
    * Changes observed in overt behaviors known to be associated with drug of abuse (hyperactivity, sedation, wet dog shakes, etc) may aid in planning other behavioral studies
  -- Drug discrimination and self-administration
  -- Other behavioral studies such as activity monitoring, rotorod test, inclined plane test, mazes, competition tests, open field test, etc.
  -- Microdialysis, brain imaging, or other neuroscience techniques
  -- Chemistry issues (chemical similarity, ease of extractability of API, etc.)

Q3: Would a change in spontaneous locomotor activity alter the subsequent preclinical strategy for abuse potential assessment, and if so, how?

- An increase in spontaneous locomotor activity suggests a stimulant profile and the possibility of abuse potential.
- A decrease in spontaneous locomotor activity suggests a sedative profile and the possibility of abuse potential.
- Thus, a change in locomotion would suggest the necessity for animal abuse studies (such as drug discrimination or self-administration).

Q4: Are hypoactivity and hyperactivity viewed differently in terms of requirements for a subsequent preclinical AP assessment?

- Both behavioral responses indicate the need for abuse potential assessments in animals.
- Hypoactivity suggests activation of receptors associated with depressant drugs (GABA, opioid, etc.).
- Hyperactivity suggests activation of receptors associated with stimulant drugs.

Q5: *What does the Agency see as the role of drug discrimination in abuse potential assessments? Does it have a use beyond selecting the training dose for self-administration studies?*

- Drug discrimination is not a measure of reward or reinforcement.
- Drug discrimination determines whether Drug X produces an interoceptive cue in an animal that is similar to the training drug. Thus, generalization by Drug X to training drug is only predictive of abuse potential if the training drug is a known drug of abuse.
- A negative signal in drug discrimination (even against a range of training drugs known to have abuse potential) does not inherently mean Drug X has no abuse potential. A unique mechanism of action in the brain may mean a unique abuse potential profile dissimilar to those of other drugs of abuse.
- Doses used in drug discrimination typically produce plasma levels similar to those produced by the therapeutic dose. Doses too low or too high can inappropriately skew results to appear negative and may result in an invalid study.
- No direct relationship methodologically between DD and SA
  - Drug discrimination is useful on its own and does not have to be conducted in order to determine doses for self-administration.
- Choice of training drug is difficult when Drug X acts by a novel mechanism. Justification of training drug selection should be based on best knowledge.

Q6: *In designing the study, should other factors be considered in choosing the route of administration?*

- Typically, the route of administration for drug discrimination studies is intraperitoneal.
- The route of administration should be chosen to simulate the exposure expected in humans. Pharmacokinetics and drug metabolism may affect the behavioral response to a drug.
- For instance, if a compound is a pro-drug and is affected by digestion or undergoes extensive first pass modification, then neither IV nor intrathecal administration would be representative.
- Similarly, drugs intended for oral use may have a different profile if administered intravenously, by inhalation, or insufflation.

Q7: Is the multiple of 3xCeff sufficient? If not what criteria should be used to set the dose range?

- The clinically effective dose is unknown at Phase 1.
- Frequently, the clinically effective dose is found to be much higher (and sometimes much lower) than initially predicted by the preclinical studies.
- Therefore, abuse potential studies should not be conducted until Phase 2 studies are completed.
- Animal abuse potential studies conducted in Phase 1 may need to be repeated if the doses used are not representative of final human therapeutic doses.

Q8: *From these results how should the self-administration training drug be chosen?*

- See the discussion on Self-Administration that follows (Slides 35 - 38).
- Doses used in self-administration are typically less than the doses that produce plasma levels similar to those produced by the therapeutic dose. This is done to prevent overdose in animals when the drug is self-administered repeatedly.
- However, a range of doses should be tested in self-administration to ensure that potentially rewarding plasma levels are achieved drug the trial.

Preclinical Pharmacology: Physical Dependence & Withdrawal

Comments on Slide 11:

- More frequent observation periods during the first 8 hr following drug discontinuation are needed.
  - Observation times should be based on the PK parameters of the drug for the species used and should be of a long enough duration to detect behaviors.
  - All behaviors should be noted and not limited to a set list of behaviors of interest. Unexpected results may alter the understanding of the drug's actions.
- One approach would be for video recording of animals during the study. Videotapes can then be reviewed for activity.
- If the indication is for females only, then abuse potential studies should include female animals.
- Tolerance is not directly related to physical dependence.

Q9: *Is cocaine the appropriate positive control?*

- FSD-204 is reported to be a “mild stimulant”, so a known stimulant should be selected as the positive control.

- The Sponsor’s selection of a positive control must be justified.

Q10: *Are the endpoints sufficient to assess physical dependence and withdrawal? If not, how should appropriate endpoints be selected?*

- Withdrawal behaviors known to be associated with drug class should be observed during discontinuation.
- For a drug with novel mechanism of action, a number of withdrawal behavior checklists derived for various classes of drugs may be useful in establishing which behaviors to look for during Drug X discontinuation.
- The presence of physical dependence (withdrawal behaviors following drug discontinuation) is not sufficient to indicate abuse potential.
- However, full characterization of a drug's abuse potential does require assessment of physical dependence.

Q11: Should both a positive control and a negative control group be included if in-house data is available to show validation of the cocaine physical dependence and withdrawal model?

- The data reported for cocaine did not show any weight loss during the drug administration phase. Given that stimulants are known to reduce feeding and to reduce body weight, this suggests that the dose of cocaine used was not high enough.

- A positive control is used to validate the study. A placebo is the only necessary negative control. The use of a false positive is not encouraged.

Q12: Is dosing for 14 days by clinical route adequate for the non-clinical assessment of physical dependence and withdrawal?

- Duration of exposure needed depends on the PK of the drug
- Appropriate duration of drug administration prior to assessing withdrawal is based on elimination half-life.
- For most drugs, a 14-day duration of drug administration should be sufficient. However, for drugs with half-lives that are relatively long, additional drug dosing may be necessary prior to discontinuation.

Q13: *What other factors should be considered when selection of the route of drug administration for a physical dependence and withdrawal study?*

- Half-life determines duration of the drug discontinuation observation period. The observation period should extend to at least 3-7 days, and it may be necessary to extend observation period if the drug is known to be eliminated slowly.

Q14: *Is there a need to target sustained pharmacological exposures, or is it sufficient to achieve this transiently?*

- Drug exposure should parallel exposure in clinical populations.
- This may depend on the intended use of the drug and the PK parameters of a drug. For instance, a drug may be intended for chronic use if steady state levels of drug are needed for optimal clinical benefit.
- Thus, if the drug product is controlled- or sustained-release, then a mini-pump may be an appropriate method for delivering drug to an animal in the physical dependence study.
- If the drug produces pharmacokinetics that peak and trough across the day, then the animal drug administration should attempt to produce a PK profile that is as similar as possible.

Preclinical Self Administration

Comments on Slide 13:

- In self-administration studies, animals are typically trained with cocaine prior to initiating substitution with Drug X. However, any drug of abuse can be used as the training drug as long as it produces levels of self-administration that are significantly different statistically from placebo.
- A positive control is a drug with known abuse potential that produces levels of self-administration that are significantly different statistically from placebo. Positive controls are often similar to Drug X in terms of mechanism of action, behavioral effects or indication. The use of a positive control provides study validation. Two examples of positive controls are amphetamine and morphine, both of which are known to be reliably self-administered.
- A negative control is a substance that produces self-administration levels that do not differentiate statistically from placebo. Therefore, placebos are effectively negative controls in behavioral studies. The use of negative controls other than placebo is not recommended for abuse potential studies.
- Note that a negative control is ***not*** a drug that produces levels of self-administration that are significantly different statistically from placebo but is not currently scheduled under the CSA. A drug with those properties is more appropriately called a *false positive* if it actually has no known abuse potential in humans. However, it is possible that such a drug could have actual abuse potential that has not been adequately characterized to date. Thus, the use of false positives is not recommended for abuse potential studies. False positives may include pseudoephedrine and diphenhydramine, which are self-administered but are not scheduled.

Preclinical Self Administration

Comments on Slide 13:

- Doses used in self-administration are typically less than the doses that produce plasma levels similar to those produced by the therapeutic dose. This is done to prevent overdose in animals when the drug is self-administered repeatedly. However, a range of doses should be tested to ensure that potentially rewarding plasma levels are achieved during the trial.

- Animal self-administration studies measure two related aspects of abuse potential:
  - Reward: If the drug produces a positive measured effect in a self-administration study for a limited time period, this may suggest that the drug can be abused by a human on a single occasion.
  - Reinforcement: If the drug maintains a positive measured effect in a self-administration over extended periods of time, this may suggest a drug can be abused by a human on multiple, closely-spaced occasions.
- Thus, if a drug produces self-administration in early trials (showing that it has rewarding properties), this is interpreted as predicting that the drug can be used successfully by humans on an acute basis to produce a “high” and that the drug may have human abuse potential.

Preclinical Self Administration

Comments on Slide 13:

- If animals maintain self-administration of a drug over subsequent trials, this is interpreted as predicting that the drug can be used by humans repeatedly over time to produce rewarding effects.

- If animals fail to maintain initially high levels of self-administration for a drug despite continued access, this can be interpreted in a variety of ways:
  - development of tolerance
  - the drug has long-lasting effects and the preferred level of effect does not require further self-administration
  - inhibition of metabolism, which can also lead to prolongation of the rewarding effects
  - development of negative effects

Preclinical Self Administration

Comments on Slide 13:

- The inability of a drug to produce reinforcement following initial indications of reward does not negate the abuse potential signal. In other words, in terms of public health, the teenager on a Saturday night using one dose of an abusable drug is just as serious a concern as the chronic drug abuser who uses increasingly larger amounts of the drug on a daily basis.

- Certain classes of drugs with known human abuse potential (5-HT2 agonist hallucinogens, cannabinoids, NMDA antagonists, and other drugs that produce effects broadly characterized as “psychedelic”) are typically not self-administered by animals. Thus, a negative result in an animal self-administration test does not necessarily mean that the drug does not have abuse potential.

- For self-administration, FR10 is the preferred schedule of reinforcement.

- Doses should proceed from low to high. If animals are exposed to high doses first, they may not self-administer the low doses as readily.

Q15: Are rats an appropriate species for self-administration studies?

- In general, rats are the preferred species for self-administration studies.

Q16: Are there specific criteria which must be met to justify the use of the rat for abuse potential assessments?

- The drug must cross the blood-brain barrier of the rat.
- If the drug produces a high degree of vomiting in humans, rodents may be an inappropriate species because they do not have an emetic response.

Q17: When rats are given the opportunity to self-administer FSD-204, they respond for 2-3 days in a burst-extinction pattern for the high dose only. How is this viewed?
Is there a minimum number of sessions that each dose of the test drug should be available for?

- A "burst-extinction pattern" is interpreted as indicating that the drug has rewarding properties on an acute basis, which is suggestive of human abuse potential.
- Duration of exposure should be at least 3-5 days

Q18: *When responding stabilizes, no increase in the infusion rates above vehicle is observed. Does this change the interpretation?*

- No. The drug appears to have rewarding properties on an acute basis.

Q19: *It is normal practice to present rat data as grouped means? Does the Agency agree that this is sufficient for such data?*

- Group means with SEM bars is adequate. However, data may also be presented as scattergrams or other methods of representing individual data in conjunction with the overall mean.

Q20: Does the Agency agree with the assessment [that no positive signals were observed in the drug discrimination, physical dependence and withdrawal or self-administration studies] given the non-clinical data supplied?

- No. The self-administration data show that the drug produces rewarding effects on an acute basis, which is suggestive of human abuse potential.

- Interpretation of data from animal abuse potential studies requires review of full protocols and full individual and mean datasets.

Proposed Safety Monitoring in Clinical Programs

Comments on Slide 16

- It is almost impossible to give special attention to CNS effects through routine collection of AEs.

- Points to consider for collecting AE data of specific interest:
  1. Correlate AEs with known or suspected mechanism of action
  2. Thoroughly review the literature for drugs with similar mechanisms of action or targets.
  3. Probing questions should be considered when evaluating adverse events that are spontaneously reported. (The terms on the following slides should be considered.)
  4. More frequent/longer evaluations of AEs should be included until the PK is more fully characterized.
  5. Prospective questionnaires should be used in later phases of development
  6. Maintain an open mind.

Abuse-Related Adverse Event Terms
Comments on Slide 16

This compilation of terms is based on our experience to date and is not intended to be inclusive of all possible abuse-related MedDRA terms. Also, not all groups of terms will apply to every drug under development.

Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The list includes:

- Specific terms that are in the MedDRA dictionary.
- Frequently used verbatim terms, words or phrases.

Euphoria-related terms:
Comments on Slide 16

- Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high[1], high*[1], high[1] feeling, laughter

- Elevated mood: mood elevated, elation

- Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey

- Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged

[1] Exclude terms that clearly are not pertinent or relevant such as “high blood pressure,” “respiratory depression,” etc.

Euphoria-related terms (continued):
Comments on Slide 16

- Feeling of relaxation: Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness

- Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy

- Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts

- Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted

Terms often associated with drugs of abuse
Impaired attention, psychomotor events cognition, mood:
Comments on Slide 16

- Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor

- Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional lability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability

- Mental impairment disorders: memory loss (excl dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders

- Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic Terms:
Comments on Slide 16

- Psychosis: psychotic episode or disorder
- Aggressive: hostility, anger, paranoia
- Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity

Q21: If there is agreement that FSD-204 is not self-administered by rats and no withdrawal signs have been observed, are there circumstances under which a Clinical Abuse Potential study in drug abusing subjects would not be required?

- There is not agreement that FSD-204 is not self administered. The self-administration data show that the drug produces rewarding effects on an acute basis, suggestive of human abuse potential.

- No data were presented regarding behaviors observed during the drug discontinuation period, so no conclusions can be drawn regarding physical dependence.

Q22: *Are there thresholds for requiring a Clinical Abuse Potential study?*

- NMEs that are CNS-acting require a human abuse potential study if there are positive signals from the preclinical data and clinical AE profile.
  - AEs observed during Phase 1 PK and dose-escalation studies and during Phase 2 dose-finding studies can provide important information regarding the design of human abuse potential studies.
  - Phase 2 dose-finding studies provide the best estimate of possible therapeutic range.

- For known drugs of abuse that are already scheduled under the CSA, a novel formulation may require additional abuse potential studies, depending on the adverse event profile observed during clinical efficacy trials.

- Therefore, it is recommended that formal studies for abuse potential be planned and conducted when the Sponsor is planning to move into Phase 3 studies. This approach will allow for selection of appropriate comparator drug(s), subject population, dose selection, and timing/duration of assessments.

AE Profile of FSD-204 following FIH Study (Table)

Comments on Slide 18:

- Given the non-existence of hallucination in the placebo group, the 2.5% rate of hallucination in FSD-treated subjects is concerning when extrapolated to the clinical population or to a drug-abusing population who may use supratherapeutic doses.

- Terms such as “dizziness” and “somnolence” are somewhat vague and do not always capture the ‘true experience’ of the adverse event. Occasionally the verbatim term does not directly map to a preferred term. As discussed above, attempts should be made to accurately capture all adverse events.

Q23: Can the Agency offer any advice regarding dose selection or other study design features to maximize chances of this study being an adequate evaluation in drug abusing population for registration?

- Individuals enrolled into abuse potential studies are healthy subjects (except for their drug abuse history) rather than patients (individuals with the disease for which the drug is targeted).

- Phase 1 studies can provide signals suggestive of abuse potential, depending on doses studied, subject population, and AE evaluation.

- Phase 2 dose-ranging studies will provide the best estimate of the therapeutic dose but only Phase 3 studies will provide the final data.

- All study phases contribute to the AE data base. The greater the number of subjects/patients exposed to different doses, the greater the ability to construct an accurate AE profile related to abuse potential. This profile allows the identification of the appropriate drug history for subjects in abuse potential studies, comparator drugs, and safety issues for the proposed doses.

Q23: *Can the Agency offer any advice regarding dose selection or other study design features to maximize chances of this study being an adequate evaluation in drug abusing population for registration?* ***(continued)***

- Prospective assessments such as subjective questionnaires may also be included in Phase 1 study design to obtain additional information that should be monitored in Phase 2/3 studies.

- Since human abuse potential studies typically use doses that are 2-3 times the highest proposed therapeutic dose for any indication, it is not advisable to conduct a human abuse potential study until Phase 2 clinical trials have been initiated with the proposed therapeutic doses.

- Communication is encouraged between the preclinical and clinical scientific staff of a company so that each group is aware of abuse potential studies being conducted and results that are observed.

Q24: Can the Agency comment on the relative importance of these criteria [mechanism, AE profile, indication] in selecting a comparator?

- The choice of a positive control for an NME, especially a first-in-class NME, with a novel mechanism of action can be challenging.

- All available data (receptor profile, AEs, and similar drugs if available) should be used to determine a comparator.

- The AE profile observed in Phase 1 and Phase 2 studies provides some of the best information on which to design a study and select a comparator.

- If an NME is the n^{th} drug in a class, comparators are more easily chosen, based on previous experience.

- A drug administered via different routes (insufflated vs oral) may have a greater risk of abuse. These comparisons (the drug against itself in different dosage forms) pose a much greater challenge for which we do not have an answer.

Q25: *How should patients be selected for FSD-204? (i.e., should they be stimulant preferring patients)?*

- Human abuse potential studies do not use patients who have the disease for which the drug is being developed.
- These studies use individuals who are otherwise healthy except for a history of using drugs of abuse.
- The drug history of the individuals recruited should include use of drugs that produce effects that most closely parallel those produced by Drug X.
- Individuals should have used the drug class of interest in the past year and state a preference for that drug class.

Q26: Is there a need to do any additional abuse potential testing in drug abusing patients – given the exposure limit and findings in the subjective effects study and given that a dose 2-3x higher than the likely therapeutic dose has not been tested, ? (i.e. would there be a need to explore higher dose range in drug abusing patients in an additional study, despite the exposure ceiling?)

- A toxicology ceiling that is less than a multiple of the therapeutic dose is of great concern, as in the case of FSD-204. For some indications, patients may expected to take additional doses inadvertently. This raises potential safety concerns.
- The phrase 'not many subjective effects in drug abusing patients' cannot be evaluated. Subjective effects in even 1 or 2 subjects may be a sufficient signal, given the relatively low number of subjects enrolled in these studies.
- For these analyses, we look at the responses of individuals, not just **mean** responses. Again, the narrow therapeutic margin for this drug raises concern that serious AEs can occur if individuals deliberately increase the dose to increase the CNS effects.
- CSS would need to have discussions with the Primary Review Division regarding the safety of this drug before making additional recommendations.

Sample Case B

Precedented chemical class with some historical evidence of abuse potential

Is there an opportunity to demonstrate that a novel member of this class does not have abuse potential?

Alternatively, if scheduling consistent with the rest of the class is acceptable to the Sponsor, what is the minimum necessary abuse potential testing?

ANX-4870 General Case Description

Comments on Slide 23

- The PK parameters, especially Tmax, are expected to be very different between the oral and intravenous formulations. This difference would be expected to affect the abuse potential of the drug.

- If the Company plans to develop an intravenous formulation, then both the intravenous and oral formulations should be tested in the clinical abuse potential studies.

Q27: Are data for CNS receptors and ion channels not commonly associated with abuse or dependence used in assessment of abuse potential?

- Yes. All information is evaluated in the review. The data on receptor modulation and receptor-receptor interactions are evolving. Therefore, CNS receptors or ion channels not currently believed to be associated with abuse or dependence may later be shown to have such an association. All data will be viewed in the context of the current scientific understanding at the time of the NDA submission.

- Novel drug mechanisms of action may be associated with previously unrecognized abuse potential in animals or humans..

- Thus, a full receptor binding profile for all CNS sites is required for both the parent drug and any major metabolite in order to determine the mechanism(s) of action.

Q28: How high should the in vitro concentrations be tested?
Q29: Should this be relative to human therapeutic plasma concentrations?

- Typically, concentrations up to 10 micromolar are tested in receptor binding studies.

- Human therapeutic plasma concentrations should be considered in the analysis. For instance, the therapeutic exposure required may be sufficiently high so as to produce adequate receptor activation, even if the receptor affinity is somewhat low.

- Generally, therapeutic doses of centrally-acting drugs do not produce brain concentrations greater than 10 micromolar. However, if the drug in development requires an especially high therapeutic dose, it is possible that higher concentrations of the drug will be necessary in receptor binding studies to parallel the concentrations produced after therapeutic doses.

Q30: *Is it acceptable to use s.c. administration for training and i.v. bolus for test sessions provided the training drug shows no difference between routes of administration?*

- The purpose of drug discrimination is to test whether Drug X produces similar interoceptive cues in an animal to the training drug.
- Interoceptive cues produced by drugs are influenced by route of administration because pharmacokinetics can vary greatly. Thus, the training drug (both at the training dose and over a full dose-response curve) and the test drug doses should be administered by identical routes of administration.
- Additionally, the training drug should be selected on the basis of having a similar mechanism of action and similar pharmacokinetics to the test drug.
- The training drug dose should be justified on the basis of similarity to plasma levels produced by the animal dose and the human therapeutic dose.
- According to the narrative, ANX-4870 is a GABA-A agonist. Thus, the selection of a midazolam as the training drug may not be optimum, given that benzodiazepines bind to a different part of the GABA receptor-channel complex (i.e., the benzodiazepine receptor).
- Drug discrimination methods that involves pain administration to an animal (stimulus-shock termination) are unnecessary and are unjustified, given that methods without pain are the current scientific standard.

Drug Discrimination
Comment on Slide 28:

- CSS reviews both individual subject data as well as group means.

Q31: Is this method of determining stable responding acceptable?

- Information should be provided regarding training drug, dose, and drug history of the monkeys used.
- It is generally inappropriate for multiple sessions to occur on the same test day, especially in the absence of information about the development of tolerance.
  - Similarly, the presence of "stability" may indicate tolerance development if self-administration decreased over the course of the testing period (whether several hours or several days).
- Self-administration data are evaluated on a day-by-day basis for each monkey in order to determine whether acute administration of a drug is rewarding to certain animals but not to others, in comparison to subacute or chronic administration. Thus, summarizing data over time is inappropriate for determining the acute rewarding effects.
- The time between drug sessions (i.e., the number of saline sessions) should be determined by the half-life of the drug. Typically, at least 4-5 half-lives are necessary before the drug is sufficiently cleared from an animal before another drug is introduced. However, if the drug produces active metabolites, the pharmacokinetics of the metabolites should also help determine time between drug sessions.

Q32: What are the merits of using vehicle sessions vs. training drug sessions between each test article exposure condition?

- The number of sessions per day seems quite high given that the drug has a half-life of 6 hr in monkeys.

- Both vehicle sessions and training drug sessions are optimally interspersed periodically between test drug sessions to ensure that animals self-administer a substance with rewarding properties or fail to self-administer a substance without rewarding properties.

Self Administration

Comments on Table Slide 31:

- All drugs should be administered at the same volume and over the same time period (infusion rate).

- The standard for the volume and infusion rate should be based on the calculations for the maximum dose.

Q33: How should the one outlier at 1.0 mg/kg be interpreted? Would follow-up studies be useful to clarify (e.g., using progressive ratio)?

- Subject A (25%) demonstrated a greater self-administration response to ANX at 1.0 mg/kg than to MDZ. This suggests that a high percentage of humans may find ANX rewarding.

- CSS would need to review the rate of response over time as well as a listing of behaviors observed during the sessions.

- Progressive ratio studies are unnecessary, once a rewarding response suggestive of human abuse potential (ie: self-administration by at least one animal) is observed.

Q34: *If the monkeys had been used extensively in previous self-administration studies, would this impact the interpretation of results with this study?*

- The drug history of an animal can alter the responsivity to new drugs. If an animal had been extensively used in self-administration studies, information should be provided regarding its exposure to drugs and how recently other drugs had been administered.

- However, it is recognized that monkey colonies with extensive drug histories can be utilized effectively for self-administration testing, if appropriate care is taken in washout periods and observation of whether certain animals have individual preferences and never choose to self-administer certain classes of drugs.

Q35: *How to balance the need for short and consistent injection durations with [the] need to explore large dose volumes for poorly soluble drugs with weak behavioral activity? Does adjusting the injection duration of the comparator to match the test article mitigate this issue?*

- The rate of injection can influence the rewarding properties of a drug. Thus, the rate of injection and the volume of injection should be identical for all drugs.

- The purpose of a self-administration study is to predict whether a drug may have rewarding properties in humans. If the drug is poorly soluble, especially at high doses, or has other practical methodology issues, a self-administration study may not be successful. A human abuse potential study may be considered a reasonable alternative.

Physical Dependence

Comments on Slide 34:

- *10% decrease in body weight gain observed at 3X human therapeutic Cmax*
- All behavioral data observed during drug administration and following drug discontinuation should be submitted.
- Behaviors of interest include not only changes in weight, but also changes in feeding, locomotor behavior, as well as unusual or unexpected behaviors.

Physical Dependence

Comments on Slide 35:

- Justification is needed for the choice of any positive control.
- Similarly, justification is needed for the choice of doses for both drugs. The drug dose should remain constant across the study and represent plasma levels similar to those produced by human therapeutic drug doses.
- Body weights should be taken daily throughout the study.
- Animals respond differently with handling. Therefore, the amount of 'interaction' with the animals should be maintained through both periods of the study.
- The functional observational battery should be 'open-minded'. While it is appropriate to have a list for guiding data acquisition, it is important to note all behavioral changes. Having a pre-specified list of behaviors does not allow for collection of unexpected events.

Q36: *Is a functional observational battery necessary or could clinical sign observations be conducted in a manner similar to a toxicology study?*

- When assessing physical dependence, behaviors should be identified in advance that are related to known withdrawal signs and symptoms in animals or humans associated with that drug class, if possible.

- Additionally, unexpected behaviors and behaviors not on the prospective checklist should also be monitored and recorded upon observation.

- When planning studies, the clinical use of the drug should be considered. If the drug is to be used intermittently versus chronically the results may differ.

Q37: *If a significant effect on body weight or FOB is observed, is there a need to establish a NOAEL?*

- The establishment of a NOAEL is not necessary.
- The purpose of assessing physical dependence is to determine whether the drug produces withdrawal behaviors following discontinuation of the drug.

Q38: *In the example presented, would a 2-week dosing interval be acceptable?*

- Presumably, the text is supposed to read “duration” or “dosing period” rather than “interval”
- Generally, a 2-week dosing duration is acceptable. However, the duration should be justified on the basis of pharmacokinetics, what is known about neurochemical regulation in the brain following drug administration and the anticipated duration of therapeutic administration.
- The dose of the drugs used should remain stable over the course of the dosing period (i.e., the dose should not increase over time).
- The dosage schedule (i.e. once daily, twice daily) and the dosing period (days to weeks) would be dependent on the PK of the drug.

Q39: *Would once per day dosing at 1.5X be acceptable?*
When is continuous infusion appropriate?

- The level of dosing (i.e. 1.5X) should be based on the clinically therapeutic dose and safety profile. A reasonable estimation of the clinically therapeutic dose should be known before undertaking some studies.

- The pharmacokinetics of the drug during therapeutic administration should determine the dosing regimen during physical dependence testing.

- Thus, continuous infusion may be appropriate if an extended release formulation is being developed, while single-dosing may be justified if the plasma levels parallel those observed in humans with once-daily dosing.

Q40: *Is a positive control necessary? If so, does the positive control have to be from the same general pharmacological class or can a standard positive control such as chlordiazepoxide be used for all NMEs?*

- A positive control can produce beneficial information that can be used in comparison with the test drug, but it is not required.

- If a positive control is to be used, it should have a similar mechanism of action as the test drug. If the test drug has a novel mechanism of action, the choice of a positive control may be justified on the basis of similarity in therapeutic indication.

- Thus, a "standard positive control" does not exist for physical dependence studies. Chlordiazepoxide should only be used as a positive control for sedative-type drugs that have similar half-lives to chlordiazepoxide.

Q41: *When is it appropriate to use a precipitated withdrawal design?*

- The purpose of a physical dependence study in animals is to predict what behaviors may be observed in humans during the drug discontinuation process. Thus, a naturalistic withdrawal period is the preferred design for physical dependence studies.

- However, precipitated withdrawal can be useful in delineating the mechanism of action of the withdrawal process and providing useful information related to the treatment of overdose and complications related to that treatment.

- Additionally, if an antagonist exists clinically for the test drug, it is important to characterize the withdrawal syndrome that will emerge if the antagonist is utilized under emergency conditions.

Q42: Would this non-clinical data package be considered complete?

- A complete preclinical abuse potential assessment requires full protocols, with justification of methodology, as well as full datasets (including mean and individual data).

- The outline of information presented here represents what is needed for the basic abuse potential package, with the caveat below.

- Summaries as presented are not sufficient for determining abuse potential.

Q43: Do the results support the interpretation?

- In the absence of a complete protocol and data package, no interpretations can be given.

- However, the graph showing that 25% of the monkeys self-administered ANX suggest that the drug may have rewarding properties.

Q44: How would this nonclinical data influence interpretation of the clinical data?

- Preclinical data are typically used to predict human responses to a drug. But human responses, including the ability to verbalize drug experiences, are a better method of determining the abuse potential of a drug than preclinical responses.

- Nonclinical data are useful for the initial understanding of the drug's actions and toxicities and to help determine dosing and adverse event monitoring. Preclinical signals of abuse potential can support similar signals in clinical studies. However, the absence of a preclinical signal can not negate clinical findings.

Q45: Could the clinical data suggest the need for additional nonclinical studies?

- The purpose of preclinical studies is to predict how humans may respond behaviorally to the drug. Thus, if an abuse signal is present in human abuse potential studies or in adverse events observed in clinical efficacy and safety trials, then the need for animal behavioral studies is obviated.

- Signals in the clinical program may raise questions that may more readily or safely be addressed in preclinical studies. New preclinical studies may be suggested by developments in the field (i.e., identification of a new isoform of a receptor of interest or new questions about metabolites). These studies may lead to a better understanding of the drug's actions and effects.

- However, if unusual behaviors are observed in humans that are not accounted for by the known pharmacology, it may be of interest to conduct further receptor binding studies if the previously-selected targets were limited.

Q46: Given the largely negative non-clinical data package, safety margins at predicted human efficacious dose and clinical Phase I AE data, would it be possible to receive a scheduling recommendation different (lower) than rest of class?

- A full abuse potential assessment of ANX-4870 cannot be completed until following a review of data submitted in the NDA. The data assessed include both animal and human data.

- We do not agree that the preclinical data are largely negative.

- The CSS recommendation to DEA concerning scheduling is determined following a complete review of abuse-related data in the NDA.

- Scheduling recommendations are dependent on the clinical safety package.

Q 47: Alternatively, if sponsor accepts scheduling consistent with the class, is it worthwhile further exposing healthy volunteers to the drug in additional clinical pharmacology studies to assess abuse potential?

- It is necessary to fully characterize the abuse potential of a centrally-active drug in order to write an accurate *Drug Abuse and Dependence* section of the product label and for CSS to be able to prepare a recommendation in support of scheduling, when necessary.

- The results of a human abuse potential study may suggest a higher abuse potential than those drugs within the class.

- Even if the Company were to accept Schedule II, abuse potential studies are necessary in order to write an accurate label.

Q47: If such studies are undertaken, how and when can Agency input on choice of comparators, test doses and endpoints be obtained? (continued)

- The choice of comparators, test doses, and endpoints could be determined by the end of the pivotal Phase 2 studies, i.e., those that determine the most likely therapeutic dose and those that have enrolled sufficient numbers of patients to provide some understanding of the AE or safety profile.

- AE data are valuable to understanding the effects of the drug and will help guide selection of comparators.

- CSS can provide input at pivotal regulatory meetings and upon request.

Q48: If different from those typically seen with the class, how would results of a standard Phase I abuse potential study in recreational drug users (with a preference for benzodiazepines) affect scheduling of ANX-4870?

- CSS is available to review protocols for human abuse potential studies at any point during Phase 2.

- We recommend that the studies not be conducted until Phase 2 or Phase 3, after proposed clinical therapeutic doses have been selected.

Q48: Would the presence of dysphoria (especially in a dose-dependent manner) critically influence a scheduling decision? (continued)

- Many known drugs of abuse produce both pleasant and unpleasant effects in humans, often at various times during drug administration.
- For example, opioids produce nausea and vomiting in many people, even in experienced opioid abusers.
- Thus, the ability of a drug to produce rewarding effects is often more important to its overall abuse potential than any unpleasant effects.

Q49: Given ANX-4870 contains a benzodiazepine-like pharmacophore, for purposes of analysis does the Agency agree the following AEs represent the clinical trial events of interest, that should be followed up as part of the trial?

-Euphoria, hallucinations, sedation, stimulation, tolerance to efficacy, morbidity/mortality with overdose

- The MedDRA AE list can serve as a basis for evaluating abuse-related behaviors during drug administration.

- However, if behaviors (AEs) not on the list are observed that are similar to those produced by other known drugs of abuse, these behaviors may also be considered relevant.

Q50: Is there a subgroup of adverse events (both reinforcing or negative) that the Agency would place a greater weight on when making a recommendation on scheduling?

- The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling.

- However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, which into which schedule the drug will be recommended for placement.

Q51: Are there mechanisms of monitoring "drug hoarding" in Phase III clinical trials that the Agency believes are credible, and whose outcomes the Agency would then take into account when scheduling decisions are made?

- We currently do not have a standard method of monitoring drug hoarding.
- The following information from clinical trials is included in the abuse potential assessment: excessive amounts of drugs reported missing, excessive amounts of replacement drug requested, plasma levels that indicate frequent "accidental dosing", suspicious stories about theft or consumption by pets, etc.
- The Sponsor should propose a method for CSS to evaluate.
- Drug hoarding could be monitored not only by pill counts but also by measurements of blood levels of the study drug.
- Blood level measurements could also provide an indication of compliance and give some insight to differences in efficacy.

Q52: In the absence of reinforcing symptoms, are there specific withdrawal symptoms in Phase III trials with ANX-4870 that would trigger scheduling?

- If human abuse potential studies and the AE profile from clinical studies do not show the presence of rewarding effects or other abuse-related behaviors or similar pharmacology with ANX-4870, a recommendation for scheduling would be unlikely.

- Physical dependence is an adaptive process in response to exposure to drugs. The presence of physical dependence is not inherently a property of drugs with abuse potential and many drugs that are known to not have abuse potential can produce physical dependence. Thus, the presence of a withdrawal syndrome in the absence of any other abuse-related signals would be unlikely to lead to a scheduling recommendation.

Q53: Is threshold for scheduling largely dependent on drug class?

- What would be the criteria for scheduling [a] drug differently from the class?

- Are there specific data that would be considered for keeping ANX-4870 unscheduled?

- The decision to recommend scheduling is based on a review of animal and human data submitted in the NDA.

- If a drug shows an abuse profile different from that of its class, then it may receive a recommendation for scheduling different from that of other drugs in the same class.

Q54: Does the Agency consider potential influence of route of administration and dosage forms when making scheduling decisions?

- Yes. Route of administration and dosage forms are relevant to assessment of abuse.

- It is relevant to the abuse potential of a drug if the drug can be abused through any route of administration, especially after manipulation of the dosage form of the proposed therapeutic preparation by a motivated user.

Sample Case C

Novel mechanism for CNS indication predominantly treated by scheduled products

What package is necessary to substantiate that the new product is different from the predecessors?

Is there a higher burden of evidence in some indications?

ADD-83 General Case Description

Comments on Slide 44:

- The observation that the metabolite does not have “in vivo activity” does not provide information on the binding profile of the metabolite.

Drug Discrimination & Self Administration Paradigms

Comments on Slide 47:

- The standards for assessing the general adverse toxicity are not known. It is possible that the drug causes toxicity that may not be obvious with intermittent periods of observation.

- The selection of dose was based on the “estimated human exposure based on AUC” and was “equivalent to an efficacy dose”. Selection of dose should be based on Phase 1 or Phase 2 data.

ADD-83 Drug Discrimination Data

Comment on Slide 48:

- Full generalization is generally considered to occur when an animal responds $\geq$ 80-85% on the training drug-associated lever.
- A lack of generalization occurs when an animal responds $\leq$ 20% on the placebo-associated lever.
- Partial generalization occurs when responding on the drug-associated lever is between 20-80%.
- In cases of partial generalization, individual data are instructive. Do all animals respond similarly, or is the partial response the result of data averaging?, i.e., some animals may show full generalization.
- Response rate has limited usefulness. If the response rate is < 50%, but when animals do manage to respond, it's all on the drug-associated lever, this still means full generalization is occurring.

Q55: *Since ADD-83 is a novel mechanism, is the DD paradigm where ADD-83 is the training drug sufficient for assessing substitution of other scheduled compounds for the indication?*

- It is preferable to utilize a training drug with known abuse potential that is thought to produce similar effects to ADD-83 and then determine whether ADD-83 generalizes to that interoceptive cue.

- Using ADD-83 as the training drug can, however, be useful in demonstrating whether there is symmetrical generalization between ADD-83 and drugs that produce similar effects to ADD-83.

Q56: Is it acceptable for DD studies to be conducted by a different route of administration from the SA studies that are typically conducted by the IV route of administration?

- DD studies typically utilize either an intraperitoneal route of administration or the proposed therapeutic route of administration.

- The reason SA studies use intravenous administration is that this process produces immediate drug exposure in the brain. This is not necessary for DD studies.

Q57: Is the strategy of identifying adverse and behaviorally disruptive effects sufficient for setting the upper dose in DD and SA studies?

- This method of determining drug doses is appropriate in situations where a drug is unlikely to be tested in humans.

- However, for drugs that are in development, the appropriate method of determining the doses for use in DD is to base them on plasma levels produced by the proposed therapeutic dose.

- Thus, a range of doses should be utilized producing plasma levels produced by the human therapeutic dose and the plasma level produced by up to 3 times the human therapeutic doses.

Q58: If IV solubility is limited for studies, is the oral route of exposure required for SA?

- The purpose of a self-administration study is to predict whether a drug may have rewarding properties in humans.
- Given that a human abuse potential study may be necessary for any drug with CNS penetration (dependent on AE profile in clinical studies), difficult drug solubility at higher doses (or other practical methodology issues) may obviate the usefulness of and need for a self-administration study.
- If intravenous dosing is not feasible, a human abuse potential study may be recommended, once safety issues, as discussed below, are resolved.

Q59: What if there is a cardiovascular effect produced by the compound that limits the dose selection for this study?

- CSS would have to discuss the safety and tolerability issues of this drug, especially in light of a dose-limiting cardiovascular AE, before the doses used for an abuse potential study can proceed.

- Some questions that we have are:
  - What is the nature of the cardiovascular AE?
  - What is the clinical implication of this cardiovascular AE?
  - How does this affect development and the therapeutic window?
  - Is this suggestive of a therapeutic window that is too narrow?

Q60: Is there a preference for the classic design where the novel compound would be substituted for a training drug like cocaine or the choice design for SA where the animal would respond for drug vs. food?

- Typically, animals are trained to a drug with known rewarding properties (such as cocaine) and then the test drug is substituted to determine whether self-administration is maintained.

- Use of the design involving choice between drug and food is difficult to interpret for regulatory purposes, since many rewarding drugs interfere with feeding behavior.

Q61: Is it acceptable to use the reversibility arm of a tox study to assess withdrawal effects?

- The reversibility arm can be used to assess withdrawal effects as long as appropriate observation of the animals is planned.
- The drug discontinuation phase of the tox study should be designed to prospectively evaluate all behaviors that may represent a withdrawal syndrome.
- A list of behaviors should include those that are part of a withdrawal syndrome from drugs in the same pharmacologic class, or drugs with the same proposed indication.

Q62: Are measures of clinical signs and body weights sufficient endpoints for withdrawal assessments?

- Clinical signs and body weights are not sufficient endpoints for withdrawal assessments.

ADD-83 Proof of Concept Trial

Comments on Slide 56:

- All AEs must be reported, not just the most frequently reported AEs.
- The small number of patients enrolled in these studies makes even single events potential signals of interest.
- The relationship between the timing of the dose(s) and the occurrence of the AE should be reported and include the duration of the AE.
- Any intervention used to manage the AE should be reported.

ADD-83 Proof of Concept Trial

Comments on Slide 56:

- The drop out rate should be reported.
- Information about the development of tolerance should be provided.
- Information about the dose relationship to the preclinical dose associated with cardiovascular toxicity should be provided.
- 'Most frequent' AEs are informative. But AEs, whether frequent or not, are considered in the review.
- VAS should have been assessed starting with first dose.
- Many drugs of abuse are used intermittently.

Proof of Concept Trial End of Study VAS on Subjective Effects

Comments on Graph Slide 58:

- Dose information is necessary to fully interpret the subjective data.
- The addition of error bars provides a sense of the variation in subjective response.
- Usefulness of the data is highly dependent on the correct population being studied.

Q63: Stopping of a medication at the end of a trial may result in a return of symptoms (loss of the drug effect), a discontinuation syndrome (e.g., SSRIs), and/or withdrawal. How should companies differentiate between these phenomena when assessing the abuse potential of drugs in development?

- A withdrawal syndrome is the pharmacological term for behaviors observed following discontinuation of a drug after chronic administration.
- The behaviors observed following discontinuation of SSRIs are appropriately termed a withdrawal syndrome.
- The presence of a withdrawal syndrome does not inherently mean a drug has abuse potential.
- Interpretation of behaviors following discontinuation of a drug (ie: is it the recurrence of symptoms the condition treated or a withdrawal syndrome?) is made during review of all data submitted in an NDA.

Q64: Methods for screening for abuse potential in POC and/or efficacy trials are not well developed. The POC in this case study attempted to utilize both a blinded discontinuation phase and a simple VAS similar to those used in trials to investigate abuse potential. Other methods that have been used include monitoring for diversion/abuse of study drug and investigation of patient reports of subjective effects and/or AEs. What methods, if any, does FDA suggest companies use in POC and/or efficacy trials to screen for abuse potential? Is this an area where better methods need to be developed?

- Psychiatric and neurological AEs (as described above with MedDRA terms) are an appropriate method of capturing abuse potential signals in humans.
- Prospective subjective scales, monitoring for diversion and abuse of study drugs and assessment of a withdrawal syndrome are all useful as well.
- Instances of diversion have been captured by detecting events that may present under ‘administrative reasons’, ‘lack of compliance’, ‘lost-to-follow-up’, ‘non-adherence to protocol’ or ‘other’ as reasons the subject/patient was discontinued from the trial.

Clinical Trial to Evaluate Abuse Potential

Comments on Slide 60:

- The basis for selecting the subject population should be described and justified.
- If patients in the Phase 2 studies experienced sedation, it may be inappropriate to use a population who preferred stimulants.
- A group who had polydrug abuse may have been a more appropriate population.
- The basis for selecting the comparators should be described and justified.

Clinical Trial to Evaluate Abuse Potential

Comments on Slide 61:

- More information is needed regarding whether the orthostatic hypotension and or sedation are related to the cardiovascular events noted previously.

- The AE “sedation” suggests that merely assessing ADD-83 as a stimulant was not appropriate.

Clinical Trial – DRQS:Do you like the drug effect you are feeling now? (6 hrs post dose AUC).

Comments on Slide 63:

- In addition to providing the ‘6 hour post-dose AUC’ for demonstrating effects, data from each time point assessed should be presented. This approach allows for detecting peak effects that may affect the interpretation of the results.

- Assessments should be made to capture information at Tmax of the drug. If multiple drugs are used with very divergent Tmax’s, then there should be several assessment periods.

Clinical Trial ARCI Amphetamine Scale (6 hrs post dose AUC).

Comment on Slide 64:

- CSS is interested in the all ARCI data collected

Q65: *Are the positive and negative controls appropriate?*

- No, according to the AE profile listed above (most frequent in clinical studies: mild sedation, orthostatic hypotension, hiccups, visual disturbance (e.g., “colors look weird”, fainting, muscle twitch), the drug effects do not resemble those produced by stimulants.

- Thus, the choice of stimulants as the positive controls (phentermine and methylphenidate) and as the false positive (pseudoephedrine) does not appear to be justified.

Q66: What is the appropriate number of positive and negative controls (both in terms of doses and drug classes) for a clinical study?

- Generally, only need one comparator drug and a placebo. Combination drug products may need additional drugs for comparison.
- The purpose of a positive control is to validate the study. Thus, one dose of one positive control is adequate.
- Use of additional positive control drugs, or additional doses unnecessarily complicates the statistical analysis of data.
- The use of a false positive is not recommended.

Q67: What methods should be used and what factors should be considered when selecting the doses for the experimental drug for a clinical study? Any drug effect vs. good drug effect?

- AEs that occur in Phase 1 and Phase 2 studies will best estimate the nature of CNS effects that occur with the study drug.

- This information should be used in selecting a comparator drug with similar effects.

Q68: *What is an adequate range of doses for a clinical study?*

- This is dependent upon the safety data from the Phase 1 and Phase 2 studies.

- A human abuse potential study typically uses doses of the drug that are 2-3 times the proposed clinical dose, if this can be done safely.

Q69: What factors should be considered when deciding on the interval between doses in a clinical study?

- PK and metabolism data.
  - The primary factor is the half-life of the drug and any active metabolites.
  - Typically, at least 4-5 half-lives should pass before another drug exposure is given.
  - Metabolic data that suggest enzyme changes (induction or inhibition) should be considered.

- Information about tolerance is also critical in determining the dosing interval.
  - If tolerance develops rapidly and is maintained for a long period after a single dose, then additional time between doses may be necessary.

Q70: Are single and/or composite endpoints acceptable? What factors should be considered in the choice of an endpoint?

- Single endpoints are preferable because they are easier to analyze statistically. Composite endpoints can obscure "good drug effects", especially if they are combined with endpoints that represent negative subjective states.

- The primary endpoints for assessment of abuse potential are those that indicate the drug produces rewarding effects and/or demonstrate similar pharmacology to a scheduled drug (positive control).

Q71: How much weight does FDA give to protocol specified endpoints vs. other information (outlier analysis, AE reports)?

- CSS considers all data – animal and human, group and individual, spontaneous and induced – when assessing abuse potential of a new drug.

Sample Case D

Precedented chemical class that is CNS penetrant, but no historical association with abuse.

How much data is sufficient to confirm that another agent if this class does not have abuse potential?

NCE4

Comments on Slide 69:

- The aim of the studies in the NDA's abuse potential assessment is to assist in determining *whether* the drug has an abuse potential relative to other scheduled drugs.
- The studies do not confirm the lack of abuse potential.

Q72: Are there elements of this in vitro/in vivo safety pharmacology profile that warrant a preclinical in vivo evaluation for abuse potential?

- No information is available regarding the human therapeutic dose of NCE4. If a very high human dose is necessary, it is possible that sufficient brain concentrations would be produced that would adequately stimulate D2 receptors.

- No information is provided regarding the binding profile of active metabolites (if any).

- Thus, it is premature to exclude the necessity for animal abuse studies. Information about physical dependence (either in animals or in humans) is required in order to write the *Drug Abuse and Dependence* section of the label.

Q73: Would considerations be different if the structure contained a tertiary amine?

- If the structure is a quaternary amine, it is unlikely it would have abuse potential because such compounds do not cross the blood brain barrier.

- Points to consider:
  - Behavioral effects in animals.
  - Metabolites and binding profile of the metabolites
  - Data available to support the “predicted human efficacious dose”
  - Adverse events profile in human trials
  - Unusual behavioral signals

- In general, structure is only useful in identifying potential similarities or differences with known drugs and predicting certain activities.

Q74: Proposal: Do not conduct Drug Discrimination and proceed directly to Self-Administration. Does the FDA agree? If not, why?

- Drug discrimination is not inherently a test that evaluates abuse potential. It can, however, indicate whether Drug X produces an interoceptive cue that is similar to a training drug that has known abuse potential or has a known mechanism of action.

- Thus, if NCE4 is an anticholinergic drug, drug discrimination can be utilized to confirm that the interoceptive cue produced by NCE4 generalizes to a known anticholinergic drug.

- In humans, drugs with anticholinergic properties can produce subjective effects at high doses that can be described as “psychedelic” (hallucinogenic).

- Typically, animals will not self-administer drugs with these properties, even if humans are known to do so. Thus, it is unlikely that a drug with anticholinergic properties would be self-administered, making such a test unnecessary.

Q75: Are proposals acceptable?

[a]-Training dose based on the 1-mo chronic toxicity

[b]-Training duration to characterize lack of discriminative stimulus (maintain training for how long?)

[c]-Route of administration

- If NCE4 is an anticholinergic drug that has no active metabolites that bind to other sites in the brain, the most appropriate method of conducting drug discrimination would be to use a well-characterized anticholinergic drug as the training drug and then determine whether NCE4 generalizes to that interoceptive cue.

- As mentioned above, the animal doses should produce plasma levels that are 2-3 times of those produced by human therapeutic doses.

- Additionally, the appropriate PK measure that should be used is not AUC but rather is Cmax.

Q75: Are proposals acceptable?

[a]: Training dose based on the 1-mo chronic toxicity

- Drug discrimination can be conducted at any dose, but the generalization is dependent on the doses of both training drug and test drug.
- We are more interested in the high doses because we presume that if a drug is abusable, it will be abused in a range of doses that includes doses greater than the therapeutic dose.
- A range of doses are typically tested for both the drug under development: typically doses that produce plasma levels 2-3 times those produced by human therapeutic doses.
- The doses chosen for studies should reflect comparable subjective effects of the training drug and test drug.
- Dose selection for test drug should be based on the predicted therapeutic dose from Phase 2 data. Clearly, the dose would be limited by the toxicity. Additional discussions would arise if there is a narrow dose window.

Q75: Are proposals acceptable?

[b]: t*raining duration to characterize lack of discriminative stimulus (maintain training for how long?)*

- Drug discrimination studies can vary greatly in the amount of time necessary to establish stable bar-pressing for the drug-associated lever for the training study.

- The assessment of whether the test drug generalizes to the training drug is generally accomplished in one test session.

Q75: Are proposals acceptable?

[c]: *Route of administration*

- Typically, drug discrimination studies use either intraperitoneal administration or the proposed therapeutic route of administration.

Q76: Is employing NCE4 as the training dose acceptable and sufficient?

Q77: Since approved compounds for the indication are not scheduled, is the choice of generalization agents acceptable and sufficient?

- As discussed above, the most appropriate method of conducting drug discrimination with NCE4 is to use a well-known anticholinergic drug as the training drug and then test whether NCE4 produces responding on the training drug-associated lever.

- Drug discrimination is not inherently an abuse potential assessment, as discussed above. Therefore, it is irrelevant whether the training drug is scheduled.

- The test drug may need to be tested against a different pharmacological drug, if Phase 2 data show a different AE profile.

Q78: Is this study design acceptable?

- In humans, drugs with anticholinergic properties can produce subjective effects at high doses that can be described as “psychedelic” (hallucinogenic).

- Typically, animals will not self-administer drugs with these properties, even if humans are known to do so. Thus, it is unlikely that a drug with anticholinergic properties would be self-administered, making such a test unnecessary.

Q79: If one or two dose levels of NCE4 demonstrate sporadic self-administration (i.e., 1 in 4 monkeys intermittently respond) it is proposed to conduct a progressive ratio (PR) evaluation to clarify this ambiguity under another schedule of reinforcement, does the Agency agree?

- In this case, a progressive ratio test is unnecessary, but the need for a human abuse potential study is likely if the AE profile in the Phase 1 and Phase 2 studies show abuse potential signals.

- Self-administration answers the question of whether a drug has rewarding properties both acutely and over time. If a drug produces sporadic self-administration in 25% of animals, this shows the drug is rewarding on an acute basis.

Q80: *In the case of very poor IV solubility can the self-administration model be omitted?*

Q81: *In the case of very poor IV solubility are other routes of administration acceptable?*

- If solubility is an issue in terms of utilizing an intravenous route, then self-administration may not be necessary. Instead, the conditioned place preference test may be a useful substitute to evaluate the rewarding properties of a drug.

Q82: Does the Agency consider this approach acceptable?

- Information characterizing the binding profile of the metabolites especially regarding sites associated with abuse potential should be provided.

- Monitoring for AEs suggestive of abuse during Phase 3 clinical trials is only one part of the clinical evaluation.
  - AEs from ALL phases of clinical development are evaluated.
  - The events that occur in the dose escalation and dose ranging studies can provide valuable information on the AEs that can occur with increased or over dosing (either intentional or unintentional).
  - All AEs are evaluated because it is impossible to fully list all possible AEs that would be suggestive of abuse potential.
  - The lists that have been compiled to-date provide a framework for evaluation, but may not be all inclusive.

- See Case A slides on suggested MedDRA terms

Q83: How and when would the Agency suggest to interact with the sponsor to review preclinical data in order to determine whether a formal clinical abuse potential assessment is needed?

- NCE4 is a new molecular entity that acts on the CNS.
- Interactions with CSS for centrally acting substances should be not later than participation in the EOP2 meeting/period. Requests for comment/meetings should be requested earlier in development if the NME is known to have similarities with substances known or suspected to have abuse potential.
- Phase 1 and 2 studies will provide further information about the adverse events profile of NCE4 which may be informative as to whether a human abuse potential study will be required.
- The human abuse potential study can not be adequately conducted until data from Phase 1 and Phase 2 are acquired, to provide information about the safety and therapeutic dose of NCE4.
- Meeting requests and correspondence with CSS should be directed through the primary review division.

Treatment Emergent AEs following Phase 2 Studies

Comments on Table Slide 78:

- The conclusion that “no signals related to diversion, misuse, abuse, withdrawal, overdose or suicide” is not supported by the data listed.

- The AE profile (memory disturbance and hallucinations) is predictable, given that NCE4 is an anticholinergic. The term “similar profile in Phase 1” should be explained: Were the AEs the same? Was the incidence similar? All the data should be presented.

- At this point, the therapeutic dose is not known. These results suggest that doubling the dose (5mg to 10mg) does not dramatically increase the peripheral effects (dry mouth, constipation, urinary retention) but causes clear CNS effects that raise concern for abuse potential – hallucination, hyperactive behavior. Other events such as somnolence, memory disturbances, and possibly dizziness would require further evaluation.

- Considerably more data (especially from a large Phase 3 trial) is needed to assess diversion. It is unlikely that small, “closed”, Phase 2 trials would provide sufficient exposure to demonstrate diversion -- unless the drug had remarkable abuse potential.

Q84: Does the Agency agree that no further clinical abuse potential testing is warranted?

- No, a case has not been made. See statements from the previous slides.
- Given that NCE4 is a new molecular entity with CNS activity, a human abuse potential study may be required depending upon the AE profile observed from Phase 1 and 2 studies.

Q85: Are there any special requests for AE evaluation in Phase III or in the NDA documentation?

- We have provided a list of suggested MedDRA terms, and NDA requirements.
  - See Case A

- The documentation provided in the NDA would be what would be required for all centrally acting drugs.

- Ideally, the data acquired by EOP2 will identify AEs of interest that will require a higher level of investigation and/or documentation to better characterize the AE.