Preclinical Abuse Liability Screening: Using The CSS-PhRMA Dialogue Sessions as a Model

David V. Gauvin, Ph.D.
MPI Research, Inc.
Please Keep the Following in Mind

What is sought in these tests [sic] is the abuse [sic] potential of a drug when the drug is used nonmedically, rather than when it is used medically under a doctor’s auspices.

How do we conduct Abuse Liability Testing?

- PhRMA – CSS Dialogue Sessions were conducted in 2006
- Cross Company Abuse Liability Consortium (CCALC) was formed in 2006
- In 2008, PhRMA and CSS developed four hypothetical case studies for detailed review
- In 2010, CSS responded to PhRMA’s four case studies – basis for issuance of FDA Draft Guidance Document
- In 2013 – Abuse Deterrent Science Meeting (CPDD)
- February 2015 – Cross-Company Abuse Liability Council (CCALC) became incorporated as a nonprofit organization
How do we conduct Abuse Liability Testing?

- April 16 & 17, 2015 - Advancements in Abuse Potential Assessments, FDA –CCALC, Bethesda MD
- August 2015 – Release of “Nonclinical Assessment of Abuse Potential for New Pharmaceuticals”
  - Editors: Carrie Markgraf – Merck
  - Thomas Hudzik – AbVie
  - David Compton – Sanofi US
How do we conduct Abuse Liability Testing?

- Three Core Behavioral Assays in the Measurement of a Drug’s Abuse Liability
  - Physical or Psychic Dependence Potential
  - Drug Discrimination
  - Self-Administration

- Under Shayne Gad’s integrated system: Chapter 10, Outline #3.j.

What does the Draft Guidance Document say about species selection?

- Page 9, “Principles of Study Design”
  - “Animal abuse potential studies use several species, usually rodents and primates”
  - Sponsors should provide (1) justification for the selection of an animal model and (2) the prior drug history of the animals selected.
• When finalized, it will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic (to be finalized by December 2015)
• It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public
• This guidance does not establish legally enforceable responsibilities
• “Should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited”.
  – Comprehensive Drug Abuse Prevention and Control Act of 1970
FDA: Guidance Document Cites

Rats vs Monkeys

• FDA: Slide 40 – CSS-PhRMA Dialogue Session
  – “rats are the appropriate/preferred species”

• EMEA Guidelines: page 6
  .....where rodent or other non-primate models are available these deserve preference above primate models
Rats vs Monkeys

• As pointed out above and by CSS at IND and NDA meetings with clients, the draft cites reference to **ICH M3 (R2)** –
  – "**the nonclinical abuse liability evaluations should be conducted in rodents.**
    Nonhuman primates should be reserved only for those limited cases where there is clear evidence that they would be predictive of human abuse liability and the rodent model is inadequate." (page 21)
Rat vs Monkey

- NHPs should only be used when it is scientifically demonstrated that none of the other non-rodent species commonly used in safety testing is appropriate for the purpose of the study.

- Scientific Committee on Health and Environmental Risks
AAALAC Policies:
Tardif, Coleman, Hobbs, and Lutz, 2013

• Repeated use of a given animal is clearly not to be justified based upon reduced animal use or costs.
• Use of species with the lowest degree of sentience is not a regulatory requirement; however, from the earliest elaborations on the concept of the Three Rs (replacement, reduction, and refinement), replacement was proposed to include replacement of more-sentient species with less-sentient species
Rats vs Monkeys

- Tox programs use similar aged rats (7-8 weeks old), same strain, from same breeder;
- Rats have no drug or experimental history
- Monkeys in the colony are of differing ages, differing country of origin, different drug and experimental histories that all must be listed in report and fully defended as to the influence they may have had on the data.

- Ator & Griffiths, Drug & Alcohol Dependence, 2003
STRONG RECOMMENDATION

• Have all protocols reviewed by CSS staff during IND meetings.

• Include full justification for selection of study design AND selection of positive control articles.

• Conduct these studies in concert with Phase II and Phase III clinical studies with knowledge of targeted $C_{\text{therap}}, C_{\text{max}},$ and $T_{\text{max}}$.

• While NOT legally-binding on the agency, CSS staff will give valuable input as to validity of study designs under current “regulatory thinking”.
ASSESSMENT OF DEPENDENCE POTENTIAL
Assessing Dependence

• “There is scarcely any agent which can be taken into the body to which some individuals will not get a reaction satisfactory or pleasurable to them, persuading them to continue its use even to the point of abuse – that is, excessive or persistent use beyond medical need.”
  • Eddy, Halbach, Isbell, & Seevers 1965

• Based on existing literature to date, a drug with a long kinetic half-life is less likely to induce dependence or withdrawal
Assessing Dependence

- Physical dependence is an adaptive process in response to drug exposure.
- The demonstration of dependence is NOT a necessary or sufficient condition for schedule control actions.
- **FDA: Slide 110 – CSS-PhRMA Dialogue Session**
  - “The presence of a withdrawal syndrome in the absence of any other abuse-related signals would be unlikely to lead to a scheduling recommendation”
Methodological Considerations in Testing Dependence Liability

• A dosing schedule that allows the maintenance of the plateau effect must be used.
• What is sought in this test is the dependence potential of a drug when the drug is used nonmedically, rather than when it is used medically under a doctor’s auspices.

• **FDA: Slide 90, CSS-PhRMA Dialogue Session**
  – When assessing physical dependence, behaviors should be **identified in advance** (based on tox studies, ibid). Unexpected behaviors and behaviors not on the prospective checklist should also be monitored.
Methodological Considerations in Testing Dependence Liability

- **FDA: Slide 95: CSS-PhRMA Dialogue Session**
  - Purpose of animal study is to predict what behaviors may be observed in humans. The naturalistic “abrupt withdrawal” design is preferred.
  - However, precipitated withdrawal can be useful to delineate mechanism of action and providing useful information related to “overdose” related treatments
  - If antagonist exists clinically, it is important to characterize the withdrawal syndrome if the antagonist is given in emergency room
3 R’s

• A detailed description of the “classic” withdrawal syndromes expressed in the species chosen to conduct these studies may mitigate the need to further expose more animals to this distressful procedure to simply replicate what we already know.

• You may be able to justify comparative review of existing literature to avoid including a positive control group in your dependence liability study package.
Positive Controls

• Compellingly similar withdrawal syndromes induced by prototypic examplars of each pharmacological class of substances controlled under the CSA already exist in the published literature appearing in peer-reviewed scientific journals: Withdrawal syndromes of the
  – Opiate type
  – Alcohol type
  – Barbiturate type
  – Benzodiazepine type
  – Cocaine type
  – Amphetamine type
  – LSD type
  – THC type
Methodological Considerations in Testing Dependence Liability

- Standard FOBs are acceptable
- Body Weights and Clinical Observations are NOT enough
- Must ensure other sensitive assays are available as “add-ons” for any and ALL suspected signs of withdrawal not easily quantified in standard FOBs (i.e., rotarod, LMA, EEG/Seizure ID).
Methodological Considerations in Testing Dependence Liability

- Duration is based on PK profile (2 to 4 week exposure)
- **FDA: Slide 157: CSS-PhRMA Dialogue Session**
  - Physical Dependence Study is required in order to write the “Drug Abuse and Dependence” section of the label.
Will Tramadol Addiction Overtake OxyContin Addiction?

The widely-prescribed prescription painkiller tramadol has tricked doctors, and in turn their patients, into thinking it is a safer alternative to what are considered stronger narcotic painkillers, such as OxyContin.

The truth is, tramadol can produce a morphine- or heroin-like high, and according to public health officials, it's in the running to compete with OxyContin addiction.

Thousands of tramadol overdose cases arrive at emergency medical centers every year, and hundreds more are seeking treatment for tramadol addiction. And just like the rising death toll from OxyContin abuse, a significant number of people are dying from tramadol overdoses.

So far, tramadol hasn't equaled the destruction caused by OxyContin addiction and abuse, but there are indications that it could. OxyContin addiction has skyrocketed across the country, and has killed so many innocent people there is even a public grass-roots movement to ban OxyContin.
Drug Discrimination

Assessment of the “subjective” or “interoceptive” properties of drugs to control behavioral choice
BUZZ

THE FIRST FEELING YOU GET FROM GRASS; THAT SOMETHING IS DIFFERENT INSIDE YOU, (I.E., A GENTLE, RELAXING FEELING WITH INCREASED SENSE PERCEPTION).

MILD HIGH

RELAXED FEELING, A SORT OF CRUISING. MUSIC VERY PLEASANT, BUT NOT INTENSE. NECKING NICE, AND TELEVISION A SHADE CLEARER. A FEELING OF WELL BEING, BUT NOT ENOUGH FOR A ROCK CONCERT.

VERY HIGH

AUDIO AND VISUAL SENSES MORE INTENSE; SHORT TRIPPING, TIME SLIGHTLY DISTORTED. MUSIC FIDELITY PERCEPTIBLY INCREASED, TV PICTURE VERY CLEAR AND COLORFUL (WHETHER IN COLOR OR NOT). GOOD FOR RELAXED AND TRANQUIL LOVEMAKING; LOVEMAKING 25% SOUL AND 75% CONSCIOUS. EATING SENSES HEIGHTENED, BUT NOT UNCONTROLLABLE (EATING WILL BRING YOU DOWN TO A MILD HIGH). STILL ABLE TO MAINTAIN UNLESS YOU GET ON A LAUGHING JAG. PHYSICAL EFFECTS: A GENTLE FEELING OF TIGHTENING OF CHEEK, CHIN AND NOSE SKIN, ALONG WITH "COTTON MOUTH", AND THE BEGINNINGS OF MILD RUSHES.

VERY STONED

YOU CAN GET LOST WALKING IN THE KITCHEN. YOU SHOULD NOT GET THIS STONED UNLESS YOU HAVE YOURSELF REALLY TOGETHER, AND ARE WITH PEOPLE YOU CAN REALLY DIG AND TRUST. SUPER SLOW MOTION, MUSIC MADE BY GODS AND GREMLINS FOR YOUR ENJOYMENT ONLY. LYRICS TAKE ON WHOLE NEW MEANINGS AND DEPTHS. LOVEMAKING IS 100% FROM THE SOUL AND THE CENTER OF THE UNIVERSE. RUSHES CAREERING THROUGH YOUR BODY, BRINGING YOU CONSTANTLY TO NEW HIGHS. IT IS A TIME TO LOVE; A TIME TO PONDER THE UNIVERSE. IF YOU CAN HANDLE THIS IN YOUR HEAD, YOU WILL GROW...
Drug Discrimination

• Estimate the extent to which a novel compound is pharmacologically similar to compounds that are already scheduled

• Virtually all drugs-of-abuse can be trained as discriminative stimuli.

• Substantial concordance between discriminative stimulus and subjective effects in humans (Preston & Bigelow 1991)
Drug Discrimination

• Shannon & Holtzman (1976, 1977) concluded that the property of a drug which enables it to function as a discriminative stimulus in the rat is analogous to the component of action of the drug responsible for producing subjective effects in man.

• An NCE that engenders complete cross-generalization with a scheduled controlled training drug is a critical factor of concern for placement under the CSA

• Powerful assay in determining schedule control actions by HHS and DEA
Drug Discrimination

- FDA: Slide 120: CSS-PhRMA Dialogue Session

- “It is preferable to utilize a training drug with known abuse potential that is thought to produce similar effects to the NCE and then determine whether the NCE generalizes to the interoceptive cue”

- The appropriate PK measure that should be used to select doses of NCE is NOT the AUC, but rather Cmax.
Drug Discrimination

• What about a drug with New Method of Action?
• By definition, the NCE has no pharmacologically similar positive control for DD training
• Must rely on therapeutic target and standard pharmacological treatment regardless of their mechanism of action, for example:
  – Migraine Headache – Target
  – MOA – unique glutamatergic mechanisms
  – Possible Training: 3 Groups, 3 Cues:
    • Morphine (C-II) – to target “pain reduction”
    • Ketamine (C-III, NMDA antagonist)
    • Fenfluramine (C-IV, 5HT – Triptans target for Tx)
Tramadol

- Fully substituted for morphine in rat DD assays
Self Administration

- The assessment of the reinforcing properties of the drug. Does drug delivery increase the likelihood of the behavior that preceded it.
The Paradigm

• To say that a NCE is “self administered” says as much about the past and present behavioral and drug contingencies and history of the animal as it does about the chemical structure of the test article.

• Provides no reliable information regarding pleasure vs aversive properties of the NCE.

• Animals will work to avoid experimenter-administered brain stimulation or drug deliveries.

• Animals will work to receive electrical foot shocks.

• Experimenter-administered drug is functionally different than self-administered drug
Experimenter-Administered vs Self-Administered Cocaine in NHPs

Equivalent Baseline
170 bpm

Equivalent Baseline
100 mm Hg
SELF- ADMINISTRATION

• FDA: Slide 84, CSS-PhRMA Dialogue Session
  – If NCE is poorly soluble, or other practical methodology issues, a SA study may not be successful
  – May need to conduct in Human Clinical Trials
  – The rate of injection and the volumes of injections should be identical for all training and testing

• FDA: Slide 125, CSS-PhRMA Dialogue Session
  – Paradigms using 2-lever choice between drug and food is difficult to interpret for regulatory purposes
  – Recommend using simple 1-lever operant assay under Fixed Ratio-10 schedule of drug deliveries.
SELF- ADMINISTRATION

• This assay is NOT pharmacologically specific.
• Animals will maintain lever press responding for drug injections from most drugs that are abused by humans – regardless of the drug used to initiate the operant response.
• Generally, we propose using cocaine as the maintenance drug – maintenance dose is selected from studies published in peer-reviewed scientific journals.
Monkeys

Stimulant Training
Cocaine DEC

Test CNS Depressant
Heroin DEC
Rats

Stimulant Training
Cocaine DEC

Test CNS Depressant
Hydrocodone DEC
Rat: Tramadol Self Administration
Recomendations

• Have discussion “in house” early in development
• Engage the Controlled Substances Staff, in CDER early in IND to discuss prospects of abuse liability (answers are not legally binding)
• If there are questions, engage the Office of Diversion Control at Drug Enforcement Administration (answers are not legally binding)
• MUST be a topic at IND review with FDA staff (not legally binding)
• Openly address the issue in the NDA application
Conclusions

• Benefit: Cost ratio of abuse liability testing is very high with respect to:
  – Labelling
  – Scheduling Actions
  – NDA Approval Process
  – Public Opinion / Reaction to abuse

• Does CSA scheduling affect sales?
  – Oxycontin, MS-Contin, Hysingla HR
  – Adderall
  – Ritalin, Concerta
Thank You

Appreciation to the Safety Pharmacology Society for its Continuing Education Program