ADDRESSING CHALLENGES IN STUDY DESIGN FOR COMPOUNDS WITH A NOVEL MECHANISM OF ACTION

Mary Jeanne Kallman, PhD, DSP

Director Global Nonclinical Neuroscience

April 16-17, 2015

COVANCE
SOLUTIONS MADE REAL™

Confidential – For Internal Use Only

How are regulatory/scheduling studies different from scientific studies?

Unique characterics?

- Abuse potential is unknown for new drugs. May need paradigms that can be used for screening
- Goal is to establish a scheduling recommendation not solely scientific characterization for known compounds
- Both nonclinical and clinical data are required to provide perspective on new drugs
- Regulatory/scheduling studies compare effects to known compounds to provide perspective
- Dose range for testing is 3X to 5X range of human equivalent blood level for upper therapeutic range (what does human equivalent mean?). Data required by EOP2 meeting!
- Scientific studies emphasis characterization of the process of dependence development with known abused compounds to a greater extent and focus on mechanism

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Are Regulatory/Scheduling Studies Designed Like Scientific Studies?

NO!

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Selection of Route of Administration

Different Routes Requirement for Different Assays

Ideal Situation

- **Dependence Studies** – by therapeutic route, typically oral, with a comparator by the same route of administration (similar to toxicology parameters – to share TK data available)
- **Drug Discrimination Studies** – by subcutaneous or intraperitoneal route. Need fast onset of action (company may not have pharmacodynamic or pharmacokinetic data by these routes) may require pilot data.
- **Self-Administration Studies** – Intravenous delivery or more novel oral or inhalational procedures that are not available at non-academic labs. May need to develop an IV formulation and characterize the PK of that formulation. Alternative model approaches

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Need for PK Data

Requirements for pre-evaluations

- Routes of administration required for the 3 studies (oral, subcutaneous, intraperitoneal, or iv) may not be known in early drug development.
- If primate studies are required, probably not the large animal choice for toxicology package. More typical that the dog would be the second species for toxicology studies. Insufficient dog data to support abuse liability testing of novel compounds
- Appropriate vehicles may not have been explored, especially the intravenous vehicle required for self-administration studies. Thus requiring additional PK data or selection of another animal model for testing.
- Studies require PK verification of plasma levels produced at level administered that lead to effects in the models

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Importance of Order of Study Conduct with Novel MOA

Why not conduct all studies in parallel?

- Drug discrimination data provides insight to comparators that might be used in the self-administration model
- Defines a discriminable dose of the compound if it is discriminated
- The discriminable dose data can impact expectancies of active doses in the self-administration paradigm
- Provides data on rate changes based on the drug discrimination paradigm

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Selection of Training Compounds for Drug Discrimination and Self-Administration Studies

Well explored Therapeutic Area vs. Novel Mechanism

- Well explored therapeutic area with scheduled compounds (ADHD) or known mechanism (opiate) -then the training drug would be consistent with the scientific literature
- Novel mechanism or novel therapeutic area – more complicated, AE directed?
- May have multiple training compounds in drug discrimination (all major abused drug possibilities, even those that are not model sensitive, i.e. hallucinogens?) – can drug discrimination data be used to identify single comparator for self-administration
- In self-administration is cocaine always used as the training compound? What about issues for sedative compounds, i.e. are they predictive in rodents, changes to FR requirements when working with compounds that reduce rates of responding?

COVANCE SOLUTIONS MADE REAL™

Confidential – For Internal Use Only

Dose Range for Testing in Industry/Regulatory Applications

Can be confusing!

Steps to identify upper range for testing:

1. Identify the upper blood level produced in humans at the top therapeutic dose (from Phase 2 clinical testing)
2. Identify what dose delivered in the preclinical studies for the subject of choice produces a similar blood level.
3. Is that dose “druggable” – is it free of significant behavioral changes and toxicity that would interfere with the interpretation of data? If not, lower the top dose to an acceptable range
4. Mid-dose and low or other doses – most effects in drug discrimination and self-administration occur over 1 to 1.5 log range.

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™

Novel Mechanism of Action Comparators

How to Identify?

- Emphasis on therapeutic class
- Other scheduled comparators in class?
- Knowledge of drug discrimination data to a wide range of training drugs if novel
- Importance of order of assay testing
- No negative comparators – vehicle is negative comparator
- May not be an easy answer

Confidential – For Internal Use Only

COVANCE
SOLUTIONS MADE REAL™