Safety Pharmacology Society:
Design and Execution of Human Substance Abuse Clinical Pharmacology Studies
Agenda Topics:

- HAL and ADF Design
- Development and Regulatory Aspects of HAL and ADF Studies
- Review of Tampering Methodologies
- Adverse Events, Visual Analog Effect Scales and Analysis
- Operational Aspects of HAL Study Conduct
- Pharmacy
- Recruitment, Retention and Medical Management of Patients

Setting a New Standard in Early Development Trials
HAL and ADF Design
Abuse Potential Assessment

January 27, 2010 Guidance: Assessment or Abuse Potential of Drugs

February 2012, FDA Decision Tree lays out the 8 Factor Analysis

January 2013 Abuse-Deterrent Opioids Evaluation and Labeling
Final Guidance Issued March 2014
(Expected Guidance to Generic ANDA submissions: end of 2015)

In general:
Clarify the differences between abuse potential (drug used nonmedically, sporadically for the positive psychotropic effects) vs addiction (chronic, neurobiological disorder w genetic psychosocial and environmental aspects characterized by impaired control over use, compulsions, continued use despite harm and craving)
Roadmap for assessment of early Identification of abuse signals: preclinical and clinical indicators used to direct human clinical trials for confirmation of abuse potential.
Human data drives product labeling, drug schedule and REMs including abuse potential narrative; warnings and precautions; risk compared to other products; possible REMS
Objectives of HAL vs ADF Clinical Studies

HAL
- Commonly referred to as “drug liking” study. Objective is to understand if the drug is more or less “liked” as compared to drug in the SAME drug class or with the SAME or SIMILAR mechanism
- Complicated regulatory pathway for protocol design (comparator, recruiting, etc.) requiring individualized consulting for each case. Not “one, check the box study;” assessment requires multiple studies in many cases
- Can/should include assessments for dependence potential: tolerance and physical dependence measured by repeat doses over a wide range to attain same effects or as an alternative, to avoid symptoms of withdrawal

ADF
- Objective: assess the ability of a formulation to be tampered and abused; many times drug development pursues 505b2 route bc they are reformulating approved drug
- Need to demonstrate efficacy, safety, biopharm (EtOH) and epidemiological studies to demonstrate ability to deter abuse
- Generic makers looking for guidance on regulatory pathway for “generic ADFs”
Clinical Development Perspective on HAL Studies

All drugs with the potential to act on the CNS are evaluated for abuse as part of the overall clinical development plan.

When: Typically conducted after “final formulation” and prior to/parallel to pivotal studies to qualify the relative risk of abuse in relevant populations.

Types of deterrent technologies: crush resistant, micro particles, agonist/antagonist, crush resistant IR, prodrug, other emerging technologies.
Controlled Substances Act (CSA)

- Department of Health and Human Services Secretary performs an 8 Factor analysis to determine controllability of drug and recommends scheduling based on medical and scientific analysis:
  - Actual or potential for abuse
  - Evidence of PD effects
  - Current scientific knowledge
  - History and patterns of abuse
  - Scope, duration and significance of abuse
  - Public health risk
  - Psychic or physiological dependence liability
  - If the substance is immediate precursor of controlled substance

- Control Substance Staff (CSS) recommends scheduling after reviewing analysis

- NIDA reviews the recommendation and FDA approves recommendation

- The HHS recommends appropriate scheduling and transmits decision to DEA

- DEA makes public announcements for comments and finalizes scheduling

- Scheduling outlines labeling, manufacturing, storage, ordering, prescribing and dispensing requirements.
**Tampering Methods and ADFs**

### Patch
- Heat
- Cutting
- Chewing, oral, dermal, sublingual
- Extraction (heat, filtration in solvent)
- Vaporization

### Types of ADFs: the extent of their effectiveness is assessed
- Physical/Chemical Barriers
- Agonist/Antagonist combos
- Aversion
- Delivery System (depots, implants)
- Prodrug
- Combination

### Tablets
- Chewing, crushing, grinding, cutting
- Removal or separation of protective layers
- Solution
- Layering: oral plus alcohol
- Extraction (heat, filtration in solvent)
- Vaporization
### Study Categories and Labeling Tiers Supported by ADF Studies:

<table>
<thead>
<tr>
<th>Study Category</th>
<th>Labeling Tier</th>
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<tbody>
<tr>
<td>Category 1: lab manipulation/extraction studies</td>
<td>Tier 1: evaluate the physiochemical barriers to abuse</td>
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<tr>
<td>Category 2: PK studies</td>
<td>Tier 2: reduce/block effect of manipulated product</td>
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<tr>
<td>Category 3: Clinical Abuse Potential Studies</td>
<td>Tier 3: evaluate for meaningful reduction in abuse</td>
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<tr>
<td>Category 4: Postmarketing Studies</td>
<td>Tier 4: reduce/monitor abuse across community</td>
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Types of Substance Abuse Assessments

In vitro and Preclinical assessments of abuse potential and behavior effects will indicate the type of clinical program to pursue, which ultimately drives scheduling and label claims.

Preclinical Assessment

- In vitro receptor binding assays
- Chemistry (formulation, dissolution, etc.)
- Animal pharmacology (self administration, drug administration)
- Impairment studies
- PK/PD relationship

Human Assessment

HNV studies
- Phase I Dose ranging

Patient studies
- Phases 2/3 in various populations in both randomized control trial and open label
- Dose range and drug alone studies

Recreational Drug Users
- Experienced in drug class and able to differentiate from placebo
Types of Adverse Events Observed in Substance Abuse Studies

Pharmacology Assessments for CNS acting compounds in opioids, stimulants, depressants, cannabinoids, and hallucinogens (positive control comparator) at doses from MED to supratherapeutic conducted in patient at controlled facility with a minimum of over night

Mood Elevation: euphoria, elevated mood, “drunk”

Abuse and Dependence Terms: dependence, abuse, diversion, intentional misuse

Stimulant Effects: agitation, aggression, anxiety, increased energy, jitter, hypervigilance, insomnia, irritability, nervousness, restlessness

Sedative Effects: apathy, asthenia, depressed consciousness, fatigue, relaxation, hypokinesia, indifference, lethargy, sedation, sluggishness, somnolence

Perceptual Effects (abbreviated list): dissociation, hallucinations and sensory disturbances
CANTABelet™

Human Abuse Liability (HAL) scales incorporated into Cambridge Cognition’s existing regulatory compliant Electronic Data Capture platform, CANTAB Elect.

The touchscreen tablet system has been used for assessing cognition in clinical trials for over 10 years

FDA 21 CFR Part 11 compliant software, procedures are fully ICH GCP compliant; established Quality Management System and ‘Best Practice’ software development life cycle; ISO9001 certified.

Successful routine audit by the UK regulatory authority (MHRA, January 2009); multiple sponsor audits, including a pre-study audit by a CRO for a HAL study in November 2012, with minor observations only

Clinical Services Framework Agreement/MSA executed with VACR (including CDA) – Cambridge Cognition services can be contracted under a work order, charged as a pass-through
How do we quantitate “drug liking”?  

The potential for drug “liking” is assessed by a variety of visual analog scales (VAS) which are either bipolar (opposite concepts) or unipolar (neutral or no effect at ONE end)

1. **Drug Liking VAS**
   - At this moment, my liking for this drug is
     - Strong disliking
     - Neither like nor dislike
     - Strong liking

2. **ARCI-49**
   - I am feeling...
     - Bad Drug Effects
     - Good Drug Effects

3. **Drug Similarity VAS**
   - I can feel good drug effects
     - Definitely not
     - Definitely so
   - I am feeling high
     - Not at all
     - Extremely

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Tier 1: In-vitro Studies

The in vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug can be manipulated, such as:

1. defeating or compromising the controlled release of an opioid from extended-release formulations for purposes of abuse by different routes of administration

2. preparing an immediate-release formulation for alternative routes of administration; or

3. separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product’s abuse-deterrent properties.
Tier 2: Clinical PK Studies

Clinical PK Studies

**BA comparison**

Test product (intact and manipulated) against ER reference (same) and/or reference IR product (generally crushed in solution)

**Study design:** open label, single dose, cross over

**Subjects:** HNV w under opioid antagonist blockade

Analysis

Cmax, Tmax, AUCs (through infinity or t and relevant times)

Mechanism is compromised when analysis shows

\[ C_{\text{max (man)}} > C_{\text{max (intact)}} \]

\[ T_{\text{max (man)}} < T_{\text{max (intact)}} \]

\[ A_{\text{UC (man)}} > A_{\text{UC (intact)}} \]

Or approaches the parameters of the crushed IR solution
Components of a HAL Study

- Protocol Design
- Subject Scales
- Subject Selection
- Time Course
- Medical Management
- Metrics / Endpoints

Abuse Assessment
Spectrum of Indications, Classes, and Study Designs in HAL Clinical Trials

**Phase 1:**
- Abuse potential
- First-in-man (SAD, MAD, “super-protocols”)
- Pharmacokinetics
- DDI and alcohol interactions

**Phase II/III and POC:** Substance use treatment
- Pain
- Cognitive impairment

Routes:
- Oral
- Intranasal
- Intravenous
- Transdermal
- Implant

Indications:
- Pain
- Obesity
- Migraine
- Anesthesia
- Sleep disorders
- Anxiety/Depression
- Neurodegenerative disorders
- Non-CNS Indications
- Addiction
- Epilepsy
- ADHD

Classes:
- Opioids
- Stimulants
- Cannabinoids
- Sedatives/Hypnotics
- Hallucinogens/Dissociatives
- NMEs
- Re-formulations
- ADFs

Other:
- Migraine
- Anesthesia
- Sleep disorders
- Anxiety/Depression
- Neurodegenerative disorders
- Non-CNS Indications
- Addiction
- Epilepsy
- ADHD

Re-formulations
- ADFs

ADTs
- Opioids
- Stimulants
- Cannabinoids
- Sedatives/Hypnotics
- Hallucinogens/Dissociatives
- NMEs
Tier 3: HAL studies: Design

Evaluate the subjective effects produced by intact and manipulated test product vs the same in ER and IR reference products

Randomized, placebo-controlled, single dose, double blind, crossover study in opioid experienced, non-dependent volunteers experienced in the route of administration

Route of administration is consistent with relevant abuse data and manipulation is based on *in vitro* test results

Challenge: dose selection, which can be clarified by a dose run-up pilot study

Screening Phase: naloxone challenge test

Pre-Qualification Phase: subjects must demonstrate ability to differentiate opioid from placebo, have appropriate placebo response and possibly others

Treatment Phase: study administered as a William Square design w washout periods dependent upon PK of opioid

Other studies may include discrimination studies (can a trained subject recognize known drug compared to placebo in a blinded setting?) or self-administration studies (subject given the opportunity to request additional doses)
Qualifying Phase and Subject Selection

Sample Size

- 20-50s
- Adjusted for:
  - Subjective assessments
  - Active control
  - Placebo control
  - Test/active size effect
  - Qualification criteria
  - I/E criteria

Criteria

- Placebo response +/- 10mm bipolar scale
- Placebo control > 15mm
- Positive control > 10mm over placebo
- Time course appropriate (<2h)
- Failure rates for screening are approx.
  30%; qualifying >30%; and treatment >5%
- Subjects likely to not complete or miss
  visits-so qualification very important
Tier 3: HAL studies: Analysis

Systemic categorization, tabulation and analysis of safety data for mood elevation, sedation, and psychotomimetic effects

Subjective effects, PK and other safety measures evaluated as a function of time post-dose:

1° Endpoints = Emax, Tmax and AUC0-t are determined along with typical PK parameters (usually difference of means) by time and treatment

2° Endpoints: wide range of VAS: drug liking, good effect, bad effect, high, take drug again, overall drug liking

Statistical plan should include:

- Group Statistics (mean, median, SE, interquartile range)
- Individual Responder Analysis
- Increases in Emax and AUE(0-t) and decrease in Tmax of manipulated formulation compared to intact may be indicative of compromised abuse deterrent ability; the same in regard to the IR formulation should also be considered
Operational Aspects
Specialized Pharmacy Needs for HAL Clinical Trials:

- Controlled Drug Substance Licenses
- USP 797 certified clean room with Class II Biological Safety Cabinet
- Negative pressure, HEPA filtered extemporaneous compounding room equipped with PowderSafe Ductless Balance Enclosure
- Comprehensive Pharmacy specific SOPs
- Extensive experience in extemporaneous and intravenous preparation, including biologics
- 24/7 monitoring of storage environment
- Electronic security access to pharmacy with video monitoring: facial recognition security
Pharmacy Expertise

HAL studies require pharmacy expertise in formulation preparation and administration routes:

• Preparation of ADF for insufflation via grinding, grating and pulverization and other methods
• Over-encapsulation of stimulants, sedative/hypnotics and opioids
• Formulation and sterilization of non-sterile cocaine HCl to a sterile parenteral solution
• Preparation of depot narcotic antagonist for subcutaneous administration
• Powder in capsule formulation and preparation to doses as low as 2.5mg
• Preferred: Pharmacists trained at the Professional Compounding Centers of America
Challenges of Subject Recruitment

- CANNOT be substance dependent or enrolled in a treatment program; Recreational users w history of occasional use and familiar w the class and route of administration
  - Three stages for filtering out unqualified volunteers: Phone Pre-Screening, Clinic Screening Appointment (outpatient), Qualification Phase (inpatient)
  - Unique challenges to each stage of recruitment: psychosocial issues, psychiatric conditions, underemployed/unemployed, high no-show rate
Phone Pre-Screening

- High fail rates for:
  - Drug rehabilitation program
  - Not enough drug use or no recent use
  - Not enough use of the “right” drug
  - Not using the drug the “right” way (nasal snorting)
  - History of psychiatric conditions
  - Hepatitis C
  - Alcohol abuse

- Ensuring confidentiality & honesty
  - “Is this a sting operation?”
  - Level of disclosure with a doctor at a screening appointment in the clinic vs. a recruiter on the phone
Outpatient Screening Visit

- High fail rates for:
  - BMI
  - Conflicting drug use history
  - Meet drug dependence criteria or reveal a history of treatment programs
  - Screening labs: elevated LFTs, GGTP
  - Exclusionary medical history: pain conditions and psychiatric comorbidities

- Additional issues with this population
  - High no-show rates
  - Lack of honesty about the amount of drug use, dependence, withdrawal symptoms, etc.

- Solution: Physician-driven interview
Inpatient Qualification Period

- Why Volunteers Fail
  - Positive UDS
    - Second chance
  - Naloxone Challenge
  - Con meds (especially OTCs)
  - Inability to tolerate comparator drug
  - Poor eVAS rater

- Population Difficulties
  - High no-show rates
  - Lack of transportation
  - Unable to contact subjects during the period between Screening & Qualification
  - Child care issues
  - Psychosocial stressors
Retention Issues During Treatment

- Confinement Periods
  - Drop outs & early terms
    - Death in the family, structured environment, day care issues
- Trials with multiple confinement periods
  - Alcohol & drug use, strenuous activity, con meds, “forget” to check back in
- Behavior issues and non-compliance with study procedures
  - On-site, full-time security staff
- Procedures can be difficult for staff and volunteers – very intensive
  - Staff: Time points are close together
  - Volunteers: Suffering from AEs (ataxia, emesis, agitation, sedation, etc.)
Questions

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