

Session 7: Pre-Market Abuse Potential Studies – Parallels for Studying Third Party Access Impacted by Packaging, Storage, and Disposal Options

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Session 7 Objectives

- Briefly describe the premarket human abuse potential (HAP) study methodology to measure in vivo drug effects
- Cite other relevant methodologies FDA uses now, such as social science research and survey research
- Discuss how existing methodologies may inform the design of novel methodologies intended to evaluate packaging, storage, and disposal options to enhance opioid safety.

Human Abuse Potential (HAP) Studies



- Objective of a HAP study of a new drug (e.g., NME):
 - To determine if test drug demonstrates similar, greater, or lesser degree of abuse potential (measuring “drug liking”) when compared to an active comparator (known drug with abuse potential) and to placebo
- A valued pre-market indicator of abuse potential
- Recommended for CNS-active drugs when nonclinical (animal behavioral) studies, clinical adverse event data, or epidemiologic data indicate a signal of abuse potential that warrants a clinical study of abuse potential

* See the guidance for industry, *Assessment of Abuse Potential of Drugs*, at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

HAP Study Design and Endpoints



- Typically enrolls recreational drug users experienced with drugs of abuse relevant to the test drug (e.g., by mechanism, or by rewarding effects)
- Sufficient study size typically 35 -40 completers
- Cross-over design for treatments administered; in-patient setting
 - Treatment arms: test drug (multiple arms to cover range of doses); positive control(s); and placebo
- Endpoints are subjective measures, assessed at multiple time points after drug administration
 - Primary: Drug Liking
 - Secondary: Take Drug Again; High; Good Effects; Bad Effects; and potentially others, as they may relate to specific drug class effects
- PK profile over time also collected, to correlate plasma levels temporally to subjective responses



Subjective Responses

- Endpoints are subjective measures, provide responses on Visual Analog Scales (VAS), which may be “bipolar” or “unipolar”
 - Bipolar VAS is anchored by Extreme Liking (score of 100) down to Extreme Disliking (score of 0) where middle of range (score 50) is a neutral response, not liked or disliked, typical of placebo treatment
 - Unipolar VAS for Drug Liking does is anchored as Extreme Liking (100) down to No Drug Liking (0), typical of placebo scores
- Statistical analyses evaluate: if positive control differentiates from placebo (validation of study); if test drug differentiates from placebo; and if test drug differentiates from positive control

HAP Studies with Abuse Deterrent Formulations (ADFs) of Opioids



- HAP studies in the ADF context* have similar design elements as studies to determine an NME's abuse potential
- For ADFs, objective is to evaluate the effectiveness of a an opioid drug product formulation in deterring abuse
- The study design is focused on a relevant route of abuse, still based on measuring subjective effects
- The statistical analysis is structured as an efficacy analysis to evaluate if ADF features affect positive or negative subjective responses, compared to placebo and to positive control (usually an immediate-release formulation of same opioid substance, with no attribute conferring abuse deterrence)

*See guidance for industry, *Abuse Deterrent Opioids - Evaluation and Labeling*, at <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>



HAP Studies of ADFs Are Route-Specific

- Category 1/in vitro studies investigate a variety of methods and tools for ADF product manipulation and provide information to appropriately design a HAP study investigating a particular and relevant route of abuse, e.g., intranasal, intravenous, or oral
- Category 3/HAP studies are designed to evaluate the subjective rewarding effects of a drug following chemical/physical manipulation of the ADF product (similar to what an individual might attempt in abusing a prescription opioid product)

Example: Designing Intranasal HAP Study of ADF Effectiveness



- Category 1 studies are conducted first and investigate, for example:
 - Resistance to crushing
 - Various forms obtainable and the tools utilized for crushing, grinding, etc tablets or capsules for sample preparation
 - Time required to prepare a sample
 - Achievable particle size
 - Sensitivities to heating, freezing, microwaving (etc.) prior to crushing
 - Amount of crushed/powdered material derived from [x] number of tablets subjects would be insufflating (i.e., snorting)
- Category 3/HAP studies have treatment arms that include prepared manipulated samples of both the test ADF product and the immediate-release positive control (non-ADF)
 - Tests whether subjects are able to snort the entire crushed sample, whether subjects can tolerate the experience and whether the subjective responses to the crushed sample differ from the positive control
- Determinations of effectiveness are based on whether the manipulated ADF formulation produces lower positive subjective responses

Example of Resulting Labeling Claims from Category 3 Studies



- Actual Section 9.2 “Summary” for an ADF
 - “The *in vitro* data demonstrate that DRUGXYZ has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that DRUGXYZ has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of DRUGXYZ by these routes, as well as by the oral route, is still possible.”
- No ADFs currently have labeling claims based on Category 4 (post-marketing) data demonstrating effectiveness to deter abuse in postmarket setting

Methodologies That May Be Applied to Evaluating Abuse Liability



- “Human Factors” testing
 - Currently, “human factors” testing is conducted to evaluate intended users’ ability to safely and effectively use a product as intended
 - Often involve studies of the effectiveness of “Instructions for Use” sections of patient labeling
- Knowledge tasks in HF studies can evaluate understanding of critical information
- HF testing is important to ensure that a product meets the end user's needs (i.e., the packaging, storage, or disposal options should not prevent appropriate use of the product by patients)

Methodologies That May Be Applied to Evaluating Abuse Liability (*cont'd*)



- FDA uses other social science and survey research investigating, for example:
 - Public perception of FDA risk communications
 - Patient comprehension of product labeling, warnings
 - Patient or prescriber compliance with labeling or other messaging
- Formal survey design is preceded by extensive qualitative research for issue understanding (analogous to Category 1 preceding a HAP study)

Methodologies That May Be Applied to Evaluating Abuse Liability (*cont'd*)

Social Science Research:

- Qualitative methods: mainly used as the basis of knowledge for design of quantitative survey research studies:
 - Literature reviews and environmental scans
 - Observation studies, e.g., ethnography, case studies
 - Focus groups
 - Interviews
 - Social media monitoring and analysis
 - Message testing
- Quantitative methods:
 - Descriptive/exploratory surveys to obtain public opinion
 - Experimental surveys, mainly related to testing of messages and predicting decision-making and behaviors



Considerations for New Studies of Packaging, Storage, and Disposal Options

- Potential “3rd party” individuals to recruit for studies may include subsets of those who abuse opioids, or individuals curious or susceptible to initiating abuse
- Can enroll those who are:
 - diagnosed as having opioid use disorder (OUD)
 - determined and frequent in their abuse patterns
 - recovered or in remission from OUD
 - less frequently, more opportunistically, engaged in abuse
 - nonusers, with opportunity, curiosity, or peers engaging in abuse
 - any of the previous subgroups, also living in a household or otherwise accessing a setting having an opioid-prescribed patient/family member/friend/roommate

Considerations for New Studies of Packaging, Storage, and Disposal Options (cont'd)



- Strategies in packaging, storage, or disposal that may allow for pre-market studies, and perhaps having endpoints or measures that are quantifiable
 - Mechanical manipulation studies of packaging/security features,
 - Research to test perceptions of packaging, storage, or disposal strategies
 - Research to investigate a cognitive or behavioral basis in deterring 3rd party Rx theft for drug abuse purposes



Summary

- HAP studies, Human Factor studies, and social science research are areas with cumulative experience on which to draw
- Pre-market studies of opioid product packaging and storage strategies may allow for claims of predicted deterrence to Rx theft for drug abuse purposes

