Methodological challenges associated with the adaptation of human abuse potential studies for ADF assessment

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Conflict of interest:

- Employee of Grunenthal USA

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- The opinions and information in this presentation are those of the author and do not necessarily reflect the views of Grünenthal

Content

General overview of the human abuse liability paradigm for ADF

Specific challenges in implementation of the paradigm

Population selection
Selection of route of administration
Positive control and dose selection
Drug preparation and blinding

Human abuse liability assessment paradigm -New Chemical Entity (NCE) vs. Abuse Deterrent Formulation (ADF)

NCE abuse liability study

Objective:
To provide information on the relative abuse potential of a new drug in humans and to contribute to the predicting the likelihood of abuse when the drug becomes available

Drug formulation and route tested
- Intact formulation
- Intended drug administration route

Abuse potential of the NCE is compared to:
- drug with established high abuse liability (positive control)
- placebo

ADF abuse liability study

Objective:
To assess the impact of the potentially abuse deterrent formulation on measures that predict how probable it is that the formulation will be attractive to abusers

Drug formulation and route tested
- Manipulated formulation
- Intended or unintended route

Abuse potential of manipulated ADF is compared to:
- non-ADF of the same drug (manipulated or intact)
- placebo

Human abuse potential study design
-New Chemical Entity (NCE) vs. Abuse Deterrent Formulation (ADF)

NCE abuse liability study

Screening

Pre-Qualification
- Positive control
- Placebo

Treatment
- 2-3 strengths NCE
- 2-3 strengths positive control
- Placebo

ADF abuse liability study

Screening

Pre-Qualification
- Positive control
- Placebo

Treatment
- ADF Opioid
- positive control (non-ADF opioid)
- Placebo

Challenges:
Population selection

NCE abuse liability study:

Occasional recreational drug users

- Non-dependent, recreational drug users who have a recent or current history of using a drug in the pharmaceutical class of the test drug and with drugs with similar psychoactive properties.
- Exclusion criteria: drug abuse

ADF abuse liability study:

- Non-dependent, recreational opioid experienced abusers who have experience with the particular route of abuse being studied

- Individuals who administer drug via the unintended routes are likely to be experienced drug users
  - Impact on drug dose and pre-qualification criteria
- Impact of ADF on opioid dependent subjects is not considered in current draft guidance

Challenges:
Selection of route of administration

NCE abuse liability study:

- Intended administration route

ADF abuse liability study:

- Selection of the route of administration should be based on the epidemiological data showing that a selected route is relevant

- What level of abuse via given route is necessary to be considered as relevant?
- Abuse patterns are highly dynamic and are adjusted as other opioids are reformulated with ADF
- How do you select the administration route for NCE in ADF or NCE with abuse deterrent properties (e.g., pro-drug) ?

Challenges:
Dose selection

NCE abuse liability study:

Treatment phase:
- Typically 2-3 dose levels of NCE from minimally effective to supratherapeutic
- 2-3 doses of positive control

ADF abuse liability study:

Pre-Qualification phase:
- Lower or equal to the lowest opioid strength used in the treatment phase

Treatment phase:
- Opioid strength known to produce high liking
- 2 dose levels of positive control

- Using a too low dose of positive control in Pre-Qualification might lead to an inadequate assessment of safety margins for the treatment phase
- Using a too high dose in treatment phase might result in celling effects and minimizing the potential to demonstrate incremental benefits from ADF
- For well characterized opioids, selecting one dose strength known to produce significant effects on subjective measures of abuse potential typically has been considered as sufficient

Challenges:
Drug preparation

NCE abuse liability study:

- Intact formulation via the intended route

ADF abuse liability study:

- Formulation must be manipulated prior to study administration
- E.g., for intranasal administration, ADF and positive control drug should be produced with similar particle size distributions based on a detailed protocol for the preparation of the samples

- No standard drug tampering methodology or standard in vitro test battery to guide drug preparation
- Limited public disclosure of methods utilized in the ADF research
- Differences is particle size may contribute deterrence effects, time and effort required to prepare manipulated the formulation should be considered in ADF assessments
- Manipulation should be “real world relevant”
- Ethical and safety concerns about administration of manipulated product via non-intended route

Challenges: Blinding

NCE abuse liability study:

- Blinding can be easily achieved with methods such as over-encapsulation or matched placebo

ADF abuse liability study:

- Study treatments should be similar between the ADF, positive control and placebo
  - Parallel design

- Subjective measures are associated with high variability thus cross-over design is more appropriate;
  - application of the parallel study design would impact effect size and sample size
- To facilitate blinding to include weight matched placebos or multiple placebo – for ADF and for positive control treatments, preferably administered using double dummy procedure

Summary and future direction

- Human abuse liability assessment of abuse deterrent formulations is a developing and dynamic area of research
- Although there are multiple similarities in the NCE and ADF abuse liability studies designs, ADF assessments pose numerous challenges
- The FDA Draft Guidance offers limited information on abuse liability assessment of delivery system or pro-drug ADF approaches
- Assessment of generics to ADF products is not discussed