Introduction: Category 1 Studies Overview

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The opinions and information in this presentation are those of the authors and do not necessarily reflect the views and policies of the FDA.

Category 1 Studies

This is the first series of studies in evaluating ADF products recommended in the guidance.

These studies should be done on the intended to-be-marketed formulation using an independent testing organization

Sponsors should:

- Explore the physicochemical properties of the new drug
- Evaluate the ease of compromising abuse-deterrent properties of a formulation by a number of approaches related to manipulation and extraction

The challenge in assessing the properties of an ADF product formulation is that with enough effect, the physicochemical properties are likely to be defeated by mechanical and chemical manipulations (i.e., new solvent, grinding, acid-base extraction of API)

Two Questions

So why do we consider this Category of studies important?

The studies provide basic information that instruct us on the various properties of the ADF product, so that we can evaluate and predict the likelihood that it can be manipulated and abused by alternate routes. This information should be used in designing Category 2 and 3 studies.

What relative value should be given to results obtained from these studies?

Category 1 studies in concert with clinical studies, including Category 2 and 3 studies, enhances predictability of pre-marketing data on subsequent abuse of the ADF product once on the market

Laboratory Manipulation and Extraction Studies

Mechanical Manipulation

Extractability and Solubility

Preparation for abuse by:

- Oral (Swallowing)
- *Chewing*
- Intravenous Injection
- Insufflation (Snorting)
- Inhalation (Smoking)

Mechanical Manipulation – suggested testing

Compare Test Product (final to-be marketed) to a Comparator

Evaluate Ease of Manipulation - Crush, Cut, Grate, or Grind.

Use a variety of tools:

Spoons, *Pill Crusher*, *Hammer*, Cutters, *Graters*, *Mortar and Pestle*, Grinders

Chewing and Cutting Simulators and Hardness Testing

Evaluate the Size of the Resulting Particles/Pieces

Resulting Powders – Particle Size Distribution Analysis

Examine Manipulation on Product and Comparator That Are Frozen or Heated (Microwave or Open Flame)

Extractability/Solubility Studies – suggested testing principles

Intact and Manipulated – Test Product and Comparator

Solvents for Dissolution:

- Commonly Available Solvents (e.g. Water, Ethanol, Vinegar, Isopropanol, Acetone, Mineral Spirits)
- Solvents with Relevant Characteristics (e.g., pH, polarity)

Conditions for Extraction

- Effect of Solvent Temperature, pH, and Agitation on Extraction
- Appropriate Extraction Times – Cover Range of 20% to 80% Extraction

Isolation of the Agonist – Purity?, Yield?

Isolation of the Free Base

Consider Differential Solubility and Extraction

- Opioid Agonists/Antagonists ADF Combination Products
- Opioid Agonist/Non-Opioid ADF Combination Products

Route Specific Studies – Intravenous Injection

Referred to as “Syringeability and Injectability” Studies

Ability to prepare a solution that can be taken into and ejected from a syringe/needle/filter to produce subjective effects upon i.v. abuse

Suggested Conditions

Intact, Cut, and Ground ADF Product and Comparator

Water as solvent – Small Volumes (1-5 mL)

Evaluate effects of extraction time as well as solvent temperature and agitation

Consider differential dissolution of the opioid from the remaining formulation.

Suggested Data to be Collected:

Achievable injection volume with different needle gauges

Amount of opioid in the achievable injection volume

Visual description of solution – Presence of excipients, particles, etc.

In Vitro Route Specific Studies – Snorting & Chewing

Snorting (Insufflation)

- Particle Size Achieved With Manipulation
- *Volume of Crushed/Ground Material*
- *Concentration of Opioid in Powder*
- Gelling on Contact With Water (Moisture)
- *Feasibility of Separating Nasal Irritants from Opioid*

Chewing

- *Tablet Hardness*
- *Chewing Simulator*

In Vitro Route Specific Studies – Inhalation (Smoking)

Vaporization Temperature for Salt and Base

Degradation Temperature for Salt and Base

Vaporization of Opioid from Test Product and Comparator

Ease of Converting Salt to a Base (acid/base extraction)

Questions For Consideration

Question 1. Category 1 in vitro testing has varied across development programs, with an emphasis on using methods to defeat the products that are formulation specific.

- Is this adequate?
- Are there methods of manipulation that should be standardized and applied to all products?
  - If yes, what approach should be taken to develop a standard set of testing conditions and methods?
- How many conditions should be studied?
- Should additional formulation-specific methods be applied?
- Are there additional considerations based on route of abuse when developing in vitro methods of manipulating the product?

Questions For Consideration

Question 2. With enough effort, it may be possible to defeat the abuse-deterrent properties of most, if not all formulations.

- Is it informative to manipulate the formulation to the point of failure of the abuse-deterrent properties?
- Is it sufficient to manipulate the formulation using common methods known to abusers?