Overview of the FDA Guidance Documents Regarding Drug Abuse Assessments

ABUSE DETERRENT FORMULATION SCIENCE MEETING

DISCUSSION OF THE FDA DRAFT GUIDANCE FOR INDUSTRY: ABUSE DETERRENT OPIOIDS – EVALUATION AND LABELING

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

Abuse deterrent formulations

- New area of regulatory science
- Many challenges
- Scientific and regulatory issues in the FDA draft guidance
- Input from stakeholders and interested parties

Concept of abuse deterrence

- Basic elements to assessing abuse deterrence were discussed in high level terms in an earlier guidance for Industry (2010)
  - Goal 1: To ensure access to drugs for medical treatment while limiting abuse and consequences of abuse
  - Goal 2: Introduce limits or impediments to abuse, as opposed to outright elimination

FDA Draft Guidance for Industry Assessment of Abuse Potential of Drugs

- Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf (Published January 27, 2010)
- Applicable to Abuse Potential Assessments
- Primary focus on NME's
- Integrates safety information from all areas of the NDA (interdisciplinary approach)

CPDD workshops on abuse deterrence 2012 & 2013

- Demonstration of abuse deterrent properties in new opioid products is a methodological challenge for Industry and FDA
  - Performing in vitro assays
  - Establishing a clinically meaningful assessment
  - Statistical issues
  - Interpreting data
  - Use of epidemiological data to confirm a clinically meaningful outcome

Proposed evaluation of abuse deterrence in 2010 guidance

- Extractability and solubility studies
  - Solvents of varying polarities and acid-base extractions
- For all dosages
  - Designed to determine whether any drugs present in the combination might be differentially solubilized and extracted and thus separated from the API
  - New formulations designed with possible abuse deterrent claims studied for relative abuse potential in human pharmacology studies
- Abuse potential of new drug product should be compared to a previously approved product (positive control)
  - Positive control can be IR product, ER product & possibly an extract of the new formulation that may not be abusable

Proposed evaluation of abuse deterrence in 2010

- Robust assessments of efficacy, safety, biopharmaceutics
  - Including alcohol and food effects
- Epidemiologic studies
- Label content:
  - Details of what should be included in the label and how to describe abuse deterrence in the label were not addressed

Abuse deterrence definition

- Pharmaceutical product is formulated so its physical or chemical properties may reduce, deter or prevent abuse
- Formulation changes impart properties that make extraction and purification of the active component difficult for abuse by another route
- Changes in the formulation might prevent inadvertent overdoses that can come about by chewing or cutting tablets to facilitate swallowing
- For “abuse deterrent” products to be an effective approach to reducing drug abuse, their development would have to apply to all drug products on the market: innovator and generic products.

Abuse deterrent features

- Inclusion of excipients that harden a pill
  - Makes difficult to crush, chew, grind, cut
- Inclusion of excipients alter consistency of tablets in solution
  - Deter API extraction and syringeability/injectability
- Inclusion of an antagonist, may be sequestered, active at non-recommended doses
  - Deter the administration of non-recommended doses by alternate routes
- Addition of a second active ingredient with aversive properties
  - Deter the administration of non-recommended doses
- Use of alternative drug delivery systems such as depot injections
  - Deter diversion

Guidance on Abuse-Deterrent Formulations

- Required under FDASIA:
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf (January 9, 2013)
- Goals
  - Outline studies needed for assessing abuse-deterrent formulations
  - Outline how FDA will evaluate those studies
  - Outline potential claims in labeling of abuse-deterrence based on data

Improving risk-benefit ratio

- Abuse deterrent features are intended to improve the risk-benefit ratio of abusable drug products
- Products with similar formulation, dosage, and PK/PD as other widely abuse marketed products would be expected to lead to widespread abuse
- Improving the formulation with abuse deterrent features may contribute in preventing public health problems and safety concerns
- New guidance applies to opioid drug products, though it may be relevant to other drug classes

Three-Tier Approach For Premarket Assessment of Formulations with Potential Abuse Deterrent Features

Data in NDA that Supports Abuse Deterrent Claims:

1. Laboratory based *in vitro* manipulation and extraction studies, syringeability, injectability, preparation of drug product for administration by other routes
2. Pharmacokinetic/Pharmacodynamic (PK/PD) studies: Assessments may depend on route of administration
3. Human abuse liability studies and statistical analysis

Summary

- The 2013 FDA draft guidance to Industry offers
  - Broad challenges as a new area of regulatory and scientific investigation
  - Detailed advice on evaluating abuse deterrence
  - Recommendations for a multi-tiered and flexible approach with the goal of having safer opioid drug products on the U.S. market
- We welcome comments on the draft guidance and recognize the need for further study aimed at improving study design and data interpretation
- Recommendations from this meeting will be considered in the final published guidance on ADF products
- We congratulate the organizers of this meeting for providing this forum for discussion