Deterrence of Prescription Opioid Abuse: FDA Perspective

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Center for Drug Evaluation and Research
Food and Drug Administration

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMMPACT-X
June 3, 2009
Arlington, Virigina

The content of this talk does not necessarily reflect the views of the FDA, and is entirely based on my own observations and viewpoints.

What Are We Trying to Achieve?

- FDA's regulatory authority includes assuring that the product label is accurate and complete
- FDA's public health mandate requires that we take all actions within our authority to address the growing public health crisis of prescription opioid product abuse

What Are We Trying to Achieve?

- To assure an accurate and complete product label
  - Data must come from adequate and well-controlled studies
  - Speculation and anecdote are unacceptable
  - Any issue of safety must have as thorough a set of analyses as necessary to provide a complete understanding of the risk

What Are We Trying to Achieve?

- The risks of the abuse of opioid drug products include addiction, overdose and death
- The degree and extent of these risks vary depending upon
  - Product potency
  - Product formulation, e.g., ease of defeating the controlled-release or abuse-deterrent features
  - Likeability of the drug substance and drug product
  - Extent of prescribing, i.e., availability
  - Availability of alternative products

What Are We Trying to Achieve?

- Can we, or should we address all of these factors in abuse liability studies?
- Should the patterns of current abuse limit the need for one assessment or another, e.g., if drug X is only abused intravenously and only by hard-core addicts and drug Y is a new formulation, e.g., a nasal spray
  - Will the new formulation result in a new set of abusers?
  - If that appears to be unlikely, can the studies be limited to those for iv abuse only?

The Regulatory Perspective

- The level and extent of the analysis is dependent on the nature of the new formulation and what is known about abuse of the drug substance.
- Current standards for labeling claims of abuse-deterrence (yet to be tested!):
  - There are four levels of possible claims:
    - In vitro physical or chemical formulation manipulation
    - In vivo PK assessment of the results of physical or chemical manipulation
    - Relative likeablility studies of manipulated product compared to intact product and, if relevant, older formulations of the drug substance
    - Demonstration of reduced abuse in the community

The Regulatory Perspective

- Formulation manipulation
  - E.g., can't be crushed, can't be extracted, can't be injected
  - Requires robust, valid and unbiased in vitro studies
  - Data describing the results of these studies may be included in the appropriate sections of the label when relevant
  - While this clearly provides an implicit claim, a disclaimer may be necessary to assure that these data are not promoted as evidence of reduced abuse liability
  - Consideration must be given to avoid "providing a road map to abuse"

The Regulatory Perspective

- Clinical pharmacology/pharmacodynamics
  - Demonstration that the product reduces drug liking in subjects with appropriate basis for assessing this factor
  - Appropriate for products with a sequestered antagonist
  - Study results would be allowed in the product label in the Clinical Pharmacology section
  - Again, a disclaimer may be necessary

The Regulatory Perspective

- Abuse-deterrent claim/indication
  - Requires robust epidemiological data supporting a change in levels of abuse in the community over a reasonably long period of time

The Public Health Perspective

- Which abuse population is being targeted?
  - College kid at a frat party
    - Physical manipulation is key
    - Not likely to be extracting
    - Not likely to be looking for the "best high" based on experience
    - But a reduction in the increasing rates of addiction, OD and death is high priority
    - So, even incremental changes, as long as supported by quality data, would be added to label

The Public Health Perspective

- Which abuse population is being targeted?
  - Long-time recreational user
    - Physical manipulation important, but less so?
    - Extractability? Depends on level of abuse, but probably not a key element as oral and nasal routes far more common
    - Likeability and availability are key
    - Again, a reduction in addiction, OD and death warrants inclusion of the data in the label

The Public Health Perspective

- Which abuse population is being targeted?
  - Hard-core addicts and dealers
    - Physical and chemical manipulation, extractability, likeability, availability and availability of alternatives are all key components
    - Population is considerably smaller and not likely to discontinue abuse no matter how extensive the efforts
    - They will still find a way to abuse opioids
    - Level of data to support an implicit claim would be quite high

Studying Abuse Liability

- In order to set standards, provide accurate labeling, maintain a level playing field for industry and assure a strong scientific basis for our decisions, we need:
  - Definitions and a classification of degrees of abuse-deterrence that are broadly accepted
  - Standardized metrics and study designs
  - Collection of in vitro, in vivo and epidemiological data through a rigorous scientific effort by industry and academia

Studying Abuse Liability

- And for an explicit "abuse-deterrent" claim or "reduced abuse liability" indication:
  - Define the study parameters that would permit assurance that the new product had actually reduced abuse in the community
  - Assure that this finding is durable
  - Continued monitoring for new signals post-marketing

How Will We Know When We're There?

- Advisory Committee meetings
- Three AC's already held for submitted NDAs
  - Transcripts available
  - Most of you attended one or more; many on behalf of FDA or industry
  - Clearly the level of scientific rigor varied
  - While we learned a lot, we also learned that there are no standards and the interpretation of the data is difficult for this reason
- New applications for abuse-deterrent products may also go to AC, but only if we think we have new questions for the committee to answer

How Will We Know When We're There?

- And, we hope to be able to take a set of recommendations to formalize this piece of the review process to AC
  - When we have an adequate portfolio of data from high quality studies to support the recommendations
  - The sooner the better