Summary and Conclusions: Additional Research Needs (Generics)

FDA Perspective

- The science of abuse deterrence is relatively new
  - Technologies (physicochemical, agonist/antagonist, aversion, delivery system, prodrug, combination)
  - Analytical, clinical, statistical methods used to evaluate these technologies are rapidly evolving
    - FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products

Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling, January 2013,

Therapeutic Equivalence

- Pharmaceutical equivalence + bioequivalence = therapeutic equivalence
- Therapeutic equivalence indicated the same clinical effect and safety profile

Dr. Andre Raw, FDA

Current Thinking (Dr. Raw)

- ADFs must be useful from a therapeutics perspective to treat pain
- ADF technology does not guarantee abuse deterrence
- Generic product should not have less abuse deterrence
- OGD will have sponsors follow a stepwise approach to evaluating generics vs. RLD
  - Performance-based testing

Dr. Andre Raw, FDA

Questions to be Answered

- Will the generics have to exactly meet each Tier statement, or will there be some flexibility based on “product specific” characteristics?
- If a generic conducts Category 1 and 2 studies and qualifies for Tier 1 and 2 labeling statements, do they still have to do a “liking” BE study?
- Will generics have to totally mimic the studies required for an NDA for these products keeping in mind that studies using BE endpoints are usually larger and more difficult to conduct?
- How will generics fulfill the labeling requirement for Category 4 (post-marketing) studies?
- Will the Category 4 post-marketing studies be considered part of the approval requirements for the application so they will not be eligible for exclusivity upon completion?
- Will FDA issue a Guidance specifying the requirements for generics to products with abuse-deterrent properties?

Penny Levin, M.S., Director Global Regulatory Intelligence & Policy; Teva Pharmaceuticals

PK/PD Analysis in Assessment of Abuse Deterrence

- What is the PK/PD analysis in development of ADFs?
- Draft guidance 2010 – “Characterization of the PK/PD properties of a…product is important for determining the abuse potential of a…product.”
- Draft guidance 2013 – “PK data should be collected to correlated with the PD outcomes.”

Megan Shram, PhD, Senior Research Scientist, INC Research Toronto

PK/PD Relationship Might Exist

- Physicochemical barrier
  - Resistance to manipulation for oral, IN and IV administration (not feasible)
- Prodrug
  - Must be cleaved systemically to liberate active moiety
  - Deterrence from IN and IV administration, and possibly oral if limited by saturable process
- Delivery System
  - Modified drug delivery to reduce diversion via multiple routes

PK/PD Might Matter Less

- Opioid agonist-antagonist combinations
  - Antagonist attenuates/reverses effect of opioid
  - Does PK of antagonist help predict response to agonist?
- Aversion
  - Aversive agent not intended to impact exposure to agonit
  - PK would NOT predict overall response to ADF
  - Might still experience HIGH from opioid; however, product not LIKED

PK/PD Abuse Correlation Conclusions

- Relationship between PK and PD of abuse potential is weak and highly variable
- Effects unrelated to opioid exposure impact subject's experience
- Clinical PD study necessary to determine potential for abuse (or its deterrence)
- PK alone cannot be used as substitute in abuse potential assessment

Do Pre-Marketing Studies Anticipate Post-Market Consequences?

A Case Study of Reformulated OxyContin

Edward Sellers, MD, PhD, President and Principal DL Global Partners, Inc.

Overall Strategy to Characterize Degree of Abuse Deterrence

Pre-Marketing

A	*In Vitro* Tamper Testing Studies	▪ Evaluate the physical and chemical properties of the reformulation
B	Pharmacokinetic Testing	▪ Determine the bioavailability and pharmacokinetic profile of tablets administered intact and manipulated (orally and intranasally)
C	Abuse Potential Studies	▪ Examine various subjective measures related to liking and abuse of the reformulation

Post-Marketing

D	Epidemiology Studies	▪ Assess real-world impact using post-marketing outcome data

Abuse Outcomes at 2 - 2.5 years after Reformulation of ER Oxycodone

Metric	Data Source	OxyContin Change	95% CI	P-Value
Abuse	RADARS Poison center exposures	-38%	(31-45)	<0.001
Abuse	National Poison Data System	-36%	(22-40)	<.0001
Abuse	NAVIPPRO drug treatment	-47%	(44-50)	<.0001
Abuse by non-oral routes	NAVIPPRO drug treatment	-70%	(68-72)	<.0001
Street price	RADARS Drug Diversion	-20%	(9 – 33)	0.002
Drug Diversion	RADARS Drug Diversion	-53%	(41-63)	<.001
Doctor Shopping	IMS	-40%	(35-44)	<.001
Fatalities	Adverse event reports	-62%	(49-72)	<0.001

Conclusions: Case Study Reformulated Oxycontin

- All of the post-marketing observations were correctly anticipated by the pre-market studies **taken together**
- Oxycontin provides a **unique** case study opportunity – however the post-marketing data and "clinical importance" are **only relevant to a point in time; one product and one opiate**
- **A comprehensive suite of pre-market studies** are necessary to merit an explicit Tier 1 or 2 claim
- Such claims **require post-marketing** study, monitoring or surveillance and may merit a Tier 3 claim in due course
- In that post-marketing epidemiological studies are so challenging to do (scientifically / logistically / cost / duration) **Tier 3 claims may be very hard to achieve since the size of effects will get successively smaller and smaller**
- For ER oxycodone products and potentially for selected studies of other opiates **Oxycontin is a useful reference comparator**
- Oxycontin has **set standards** for Study Types and Labeling and Claims

Panel Discussion