Drug Labeling: Comments, Conclusions & Recommendations for Guidance
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1. **Acknowledgment:** These reflect informal input from my panel via email, oral comments, and today's panel discussion. They reflect comments from others at this meeting (oral and via index cards)

2. **Apology:** I am responsible for translation to these slides

3. **Disclosure:** I am Vice President for Research, Health Policy and Abuse Liability at Pinney Associates which provides consulting support on abuse liability, abuse deterrence, drug scheduling, REMS and other challenges associated with CNS drugs

AD: Fang by Fang

Reducing tamperability to increase abuse deterrence is like de-fanging a beast fang by fang

FDA’s goal for opioids & other addictive drugs: Drugs without “abuse deterrent” designs go the way of cars without seat belts and shatter-resistant windshields – An incremental process

Approval of AD claims for generic products

1. What is the minimum amount of data needed?
2. What types of data are needed in addition to traditional “bioequivalence” data?
3. What are the relevant Pk parameters to consider, Tmax, Emax, Cmax, AUC at different points in time?
4. Tamper/in vitro studies under which conditions?

Extension of Abuse Deterrence Guidance to other drug classes

1. FDA has already signaled, implicitly and explicitly, that the AD Guidance should be considered in development of drugs in other classes – this is consistent with comments in the Chemistry section of the 2010 Abuse Potential Guidance as pertains to the science base for the Abuse Potential section of the NDA
2. Is the tiered label proposal applicable to stimulants, sedatives and other CNS drugs?

What post-marketing surveillance will reassure FDA that the risks of granting Tiered Labels are adequately minimized?

1. Beyond the Supreme Court Precedent: In the final guidance please do more to signal the likely time and nature of data that FDA will be looking for to grant Tier 4 claims
2. What kinds of data that are not currently being collected would provide additional reassurance to FDA to support Tier 4 claims?

Tiered labeling implied benefits to patients as well as to reducing abuse and overdose risks by nonpatients

1. The Tiered Labeling seems very focused on the deterrence of abuse, and this would imply a special benefit for non patients
2. In fact, the same improvements may reduce inadvertent/accidental overdose risks by patients, and children and confer other benefits
3. Does FDA see value in communicating those benefits – NOTE: if FDA's intent is to encourage prescribing & use (and payer reimbursement) such benefits may be critical to communicate

Relieving Pain in America (IOM, 2011)

1. It would seem to be an equally important goal of FDA to contribute to more effectively and broadly "relieving pain in America" as urged by IOM, as to reducing abuse and overdose
2. Can the guidance make this goal more explicit, perhaps to help encourage reimbursement of AD medications that may be more expensive than those that provide equivalent pain relief

Coordination with broader drug abuse prevention and treatment and other drug control efforts

1. Most of us would agree that in the long run drug abuse is more likely to be more effectively addressed by increasing replacement of AD drugs with non AD drugs EVEN if in the short term this results in some increase in abuse of certain illicit drugs (e.g., increased heroin) use – yet this “benefit” is troubling to many
2. What is the FDA doing, perhaps that can be announced independently of the Guidance, to harmonize its efforts with those of agencies focused on illicit drug abuse?

Generic Challenges: Encouraging generics vs. discouraging investment in innovation

1. What will be the standards for granting AD labels for generics that do meet FDA's dual goals of encouraging generic adoption of AD technology without discouraging investment in innovation?

How to Adequately Address Differences Between Formulations in In Vitro and In Vivo Studies

1. Similar in vitro studies regardless of the formulation differences, or different studies conducted?
2. In in vivo studies, does one conduct studies of tampered product using the same particle sizes, or tampered product based on in vitro findings?

Can FDA illustrate variants on Tiers that might reflect selective but important benefits

1. If a product was highly AD for a particularly deadly addictive route, e.g., smoking & injecting but offered little benefit for other potential routes of abuse might this be recognized? - this might be relevant to other drug classes, e.g., stimulants and sedatives
2. E.g., a product might be crushable and confer a potential benefit to some patients but still be general AD, whereas crushing another product might be irrelevant to its AD potential, still other products might combine multiple AD mechanisms and benefits

The Importance of Striking the Right Balance (Sweet Spot) in time and amount of data burdens required to achieve Tiered Labels

1. FDA is justifiably concerned that premature Tiered labeling actions may (with “hindsight”) be found to have resulted in more abuse and OD deaths by driving prescribing to a drug that was not actually safer
2. However, delaying tiered labeling may lead to abuse and deaths that might have been avoided if the label and associated actions were granted earlier (e.g., delaying the OxyContin action by 1 year would have likely resulted in more deaths and abuse than occurred)
3. Has the agency thought about how to quantify the risk balance and when to act?

Relationship between science to support Tiered Labeling & Scheduling Recommendations

1. The 2010 Guidance urges collection of tamper types of studies to inform abuse potential and scheduling recommendations in the Abuse Potential section of the NDA. Some of these studies are the same as those described in the 2013 Guidance to support AD claims.
2. How will drug scheduling and Tiered labeling recommendations be developed at FDA for new molecular entities vs. for previously approved and scheduled molecules?

FDA Letter to ER/LA REMS NDA holders Postmarketing requirements in Section 505(o)

1. Some of these studies are similar to those that would likely be required to support Tier 4 label claims
2. How should studies done to address the 505(o) requirements be harmonized with those intended to support Tier 4 labeling?
3. Can the guidance comment on FDA's thinking of the relevance of studies intended to comply with 505(o) address Tier 4 labeling claims and vice versa?

IR vs. ER Opioids

Please address whether FDA intending to discourage ER/LA opioids and if so how is this consistent with its efforts to encourage AD opioids, given that we will likely have more examples of ER/LA opioids with AD properties

See Language in FDA Sept. 10, 2013 opioid safety related announcement: *"Given the serious risks of using ER/LA opioids, the class-wide labeling changes, when final, will include important new language to help health care professionals tailor their prescribing decisions based on a patient's individual needs."*