Tufts Health Care Institute
Program on Opioid Risk Management
Guidelines for the Development of Abuse-Deterrent Opioid Formulations
November 9 – 10, 2006; Executive Summary

1) INTRODUCTION. N. KATZ reviewed the accomplishments of the THCI Program on Opioid Risk Management, which include one published paper ("Foundations of Opioid Risk Management"), one submitted ("Challenges in Development of Abuse-Deterrent Formulations (ADFs)"), and a third drafted ("Best Practices in Opioid Risk Management"). The October 2005 meeting served to clarify FDA's current thinking on development of ADFs. For the current meeting, two major purposes were: i) developing a Citizen's Petition (CP), requesting a guidance document (GD) from the FDA on the development of ADFs and ii) drafting a related background paper, a version of which will be published in the peer-reviewed literature. Dr. Katz reiterated that prescription opioid abuse consists of distinct sub-phenomena, including conversion of modified-release formulations into immediate-release preparations for administration by various routes (oral, inhalational, intranasal, intravenous), ingestion of formulations leading to overdose or death, co-ingestion of intact or compromised formulations with alcohol or other intoxicants); thus deterring each type of abuse will require specific formulations and supporting evidence to demonstrate efficacy.

2) ELEMENTS OF A GUIDANCE DOCUMENT (GD) FOR ADFs. C. McCORMICK reminded participants that FDA has authority to stimulate development and commercialization of ADFs by granting incentives such as guidance, protocol assistance for pivotal clinical trials, Fast Track Status and Priority Review for NDAs, and meaningful labeling. Additional incentives requiring Congressional legislation include marketing exclusivity, extension of the three year non-patent exclusivity period to five years, reimbursement guarantees, and tax credits for clinical trials. FDA can propose such legislative remedies to Congress, and recommend inclusion of incentives in the reauthorization of PDUFA.

3) POLICY AND ADVOCACY INITIATIVES. A. BARTHWELL emphasized that background papers and CPs are necessary, but to mobilize FDA in a timely fashion, a parallel policy and advocacy initiative, that involves building support among members of Congress, is required. She detailed several approaches for accomplishing this goal, and concluded by summarizing how her consulting firm, EMGlobal, and their collaborating lobbying group, DCBA Law, advocate on the Hill for specific issues.

4) REPORTS FROM LEADERS OF THE SEVEN BREAKOUT WORKSHOPS:

a) **Benchtop assessment of "extractibility"**: R. BIANCHI discussed standards for assessing the extractability of prescription opioids, as applied to ADFs. In general, because multiple types of opioid formulations exist, there is no one-size-fits-all set of assessments. Sponsors should report on product weaknesses such as solubility in readily available solvents, volatility of opioid in the formulation, impact of physical manipulations (crushing; varying temperature to accelerate delivery; using physical stress, or microwave), and sophistication of procedures required to extract active ingredient. The amount of aversive components or antagonists that carry through the extraction should be sufficient to deter abuse. An explicit claim could be that the product has been formulated to resist tampering by certain techniques (crushing, thermal stress); however, explicit labeling will need significant negotiation with the agency.

b) **Preclinical abuse liability testing of ADFs**: W. SCHMIDT discussed the applicability of current tests for assessing NDA abuse liability to ADFs. Preclinical studies should include tests for physical dependence, which may reveal safety and efficacy of *opioid antagonist-containing products* for decreasing euphoria or precipitating withdrawal. Also important are tests for single dose substitution (preventing withdrawal from a reference analgesic like morphine), reinforcing effects (does animal self-administer), and drug discrimination (differentiating between reference compound and ADF). A caveat is that good data on oral abuse liability tests for most reference opioids are unavailable. Potential claims emerging from use of new ADFs would have to be validated with preclinical studies.

c) **Analgesic clinical trials for measuring abuse liability**: B. ROUNSAVILLE discussed two types of abuse liability trials for ADFs: i) Trials for primary approval, demonstrating safety and efficacy of the ADF *as an analgesic*: For reformulated opioids, a single RCT for efficacy is generally sufficient. PK data are sufficient if the new drug and innovator are bioequivalent, but if an added active ingredient alters bioequivalency, or might compromise safety/efficacy of parent product, then efficacy trials are needed. New products require safety trials. No new ADF-type claims are expected from primary trials. ii) Trials to support ADF-type claims: Outcome measures related to abuse include patient self-report of drug use, physician aberrant behavior checklist, urine toxicology, prescription monitoring program data, "ambiguous

medication handling events", patient questionnaires, and others. No explicit claims for abuse-deterrence are likely, but trials might lead to implicit claims in the clinical pharmacology section.

d) Human abuse liability testing: S. COMER noted that information on detecting abuse liability signals for known chemical entities, and in preclinical/Phase I studies for NCEs, is found in the literature. Bench top testing would guide the use of specific tests. Standard abuse liability tests should be generally addressed (untampered/ tampered ADF produces less euphoria than tampered/untampered comparator, abuse-deterrent ingredients are effective, prodrugs have desired PK-PD profile). Product PK, route of administration, study population, self administration, relative cost of tampering and level of expertise needed should also be addressed. Potential claims would address drug liking (lower for drug X than for control Y), and effects of self-administration (lower for drug X than for drug Z).

e) **Alcohol interaction human studies**: E. SELLERS discussed studies on the potential interactions between ADFs and co-administration of alcohol; these include PD measures, and can be useful in establishing the clinical importance of *in vitro* interactions with alcohol. Extensive literature provides the basis for design and conduct of such studies. For ADFs, ethanol effects on all active components must be considered. The proposed ADF GD should specify criteria for which *in vitro* studies require an *in vivo* study, when PK-PD findings are not clinically significant, or when they reveal a clinically meaningful protective effect of the ADF if taken with alcohol, and what magnitude of an alcohol effect defeats the abuse deterrent properties of the ADF. Necessary controls should be spelled out. Conditions for conducting PK-PD alcohol interaction studies for formulations by generic companies should also be specified. Conclusions drawn from PK-PD studies must be related to data on actual patterns of alcohol and specific medication use, in order to anticipate the public health importance of any interaction risk. The following two kinds of label may be possible: an existing class label, similar to the one currently applied to immediate release morphine ("Warning: Should be used with great caution in a reduced dosage in patients receiving CNS suppressants including alcohol") or an enhanced or boxed warning risk "Label Option B" ("Patients must not consume alcoholic beverages or prescription or nonprescription medications containing alcohol while on Product X. Co-ingestion of alcohol with Product X may result in increased plasma levels and a potentially fatal dose of component Y.").

f) Epidemiologic studies: E. ADAMS discussed post-approval labels which could say "Product X is associated with lower prevalence of abuse than other formulations with same active ingredients", or "Product X is associated with a lower prevalence of IV administration than other formulations containing the same active ingredient". Supporting epidemiologic studies could include comparators using active ingredient and other drugs in the same Schedule and in target Schedule for ADF; indicators of abuse, addiction and diversion, and active surveillance for adverse events and diminished efficacy; populations with known abuse risk factors, comorbidities, and pharmacogenomics. A condition-based registry study (e.g., for chronic pain), retrospective studies in sentinel street populations, studies of physicians (as sentinel population and as source of information about drug access and reactions), diversion studies, and studies of surveillance systems are also needed. To support the conclusion that product X is less abused intravenously, less abused overall, etc. a large multi-year registry study would be needed, including two comparators in a different schedule than the drug (e.g., oxycodone versus hydrocodone), and some measures of diversion and the development of abuse patterns in the patient population. Documenting lower abuse potential with thousands of people on the street implies a long-term study, which may be unacceptable to the sponsor because of the expiry of exclusivity. The length of the study, and whether it could begin premarketing could be negotiated with the FDA

POLICY AND ADVOCACY AGENDA FOR THCI P-ORM. A. BARTHWELL reiterated points made in earlier talks, that the CP should be written to induce FDA to produce a GD, and should specify that ADFs will avoid unnecessary pain and suffering deriving from abuse and diversion, and improve patient access to effective medications. There will be a greater requirement for postmarketing surveillance with ADFs, and the FDA can provide incentives for innovation, development, and commercialization of new ADFs. The CP could request removal of older, more abused compounds from the market, once something new comes on to the market (but maybe this is better left up to the marketplace?). We should work to have Congress authorize industry-focused incentives to develop and commercialize ADFs, such as guaranteed reimbursement for these medications (to cover costs of development and testing), tax incentives to reduce the development cost to industry, provisional scheduling for a new formulation which could be retained if the post-marketing surveillance held up the claims. We should also approach the DEA with regard to differential scheduling (post-market).

IMPORTANT MISCELLANEOUS ISSUES

- How should generics be treated? If a generic equivalent is developed for an ADF based on a PK equivalence approach, but the generic does not have the same safeguards as the ADF, should the generic be allowed any ADF-type labeling?
- If ADF labeling requires long-term epidemiologic studies, drugs approved with only 3 years exclusivity will generate little motivation to conduct these studies, unless they can be started premarketing and completed expeditiously (such as a registry study).
- Scheduling is important but should, for practical reasons, be disentangled from the FDA guidance.

THE NEXT MEETING:

- Scheduled for March 29-30, 2007; probably in Boston.
- Topic: “What to do when you see a signal in prescription opiate abuse surveillance”.