Executive Summary

THCI Meeting on

MANAGEMENT OF SIGNALS RELATED TO PRESCRIPTION OPIOID ABUSE

March 2007.

Abbreviations used:

ASI-MV	Addiction Severity Index – Multimedia Version
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
FDA	Food and Drug Administration
FDAAA	Food and Drug Amendments Act
IOM	Institute of Medicine
MTF	Monitoring the Future
NADDI	National Association of Dug Diversion Investigations
NIDA	National Institute on Drug Abuse
NSDUH	National Survey on Drug Use and Health
POA	Prescription Opioid Abuse
RADARS	Researched Abuse Diversion and Addiction-Related Surveillance
REMs	Risk Evaluation and Mitigation Strategies
RM	Risk Management
RMPs	Risk Management Programs
TEDS	Treatment Episode Data Set
TIP	Treatment Improvement Protocols

Access to prescription opioids alleviates suffering for millions of Americans, but is correlated with a marked increase in the abuse of these analgesics. Many abusers get opioids from doctors' prescriptions or from friends/family: opioids are perceived to be safe, and decoupled from the law enforcement monitoring that is associated with illicit products such as heroin or cocaine. However, growing awareness of such abuse affects prescribing patterns, and threatens to deprive legitimate patients of effective pain relief. In response to public health concerns about prescription opioid abuse (POA), Risk Management Programs (RMPs) have evolved, which are systematic efforts targeted at detecting and reducing abuse, while maintaining appropriate access to therapy; RMPs encompass surveillance (monitoring for indications of abuse), signal detection (determining whether such indications exist), field investigation (characterizing the nature of signals and potential interventions), and intervention (deploying measures to mitigate signals). *This meeting was aimed at better understanding signal management: responding to a "signal" about POA, developing signal management algorithms for pharmaceutical companies, designing signal assessment studies and ensuing interventions, and articulating policy considerations based on collaborations between pharmaceutical companies and other key stakeholders.*

I. Risk Management (RM). *First generation Risk RMP's* (1970's) were statutory programs targeted at preventing abuse of medications (e.g., methadone) for treating opioid and nicotine addiction. *Second generation RMP's* (1990's) evolved to prevent specific risks with nicotine replacement products in unintended populations (nicotine replacement products becoming a gateway to smoking among teenagers), and to contain buprenorphine abuse. Product surveillance by sponsors was required for FDA approval, and prescribing physicians had to be DEA registered. *Third generation RMPs* (2001), were launched in response to OxyContin abuse, and expanded FDA focus to all identifiable product risks, including misuse and abuse. In the aftermath of the IOM report (2001), Federal agencies monitoring opioids all emphasized RM, defined by the FDA as "an iterative process of assessing a product's benefit-risk balance, developing and implementing tools to minimize its risks while preserving benefits, evaluating tool effectiveness and reassessing the benefit-risk balance, and making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance". Three FDA Guidances (2005) on RM also endorsed continual assessment of signals and interventions, and highlight the need for signal management. Since passage of the FDAAA legislation (2007), RM efforts, termed Risk Evaluation and Mitigation Strategies (REMS), fall under the authority granted by the legislation.

II. Signal Management: Detection, Prioritization, Assessment. Signals indicate that something (unexpected) is occurring, and are often based on statistically significant deviations from baseline expectations. Pharmacovigilance uses traditional information sources (health care providers, patients, pharmacists, sales/field representatives, media reports, published literature) to detect signals, but may also draw on other sources such as the Internet (drug sale sites, MySpace, Facebook, user blogs, List Servs such as NADDI or RxPatrol, chat rooms), law enforcement (federal, state, local), media reports (national, local), federal surveys (DAWN, NSDUH, MTF), poison control centers (TEDS, RADARS, ASI-MV-Connect), drug abuse treatment programs (TEDS, RADARS), regulatory boards, and key informants (health care professionals, patients in treatment programs, methadone maintenance specialists, pain patients, pain management specialists, NIDA) to gauge abuse/diversion outside the doctor-patient relationship. Signals may be of various types (sentinel events, sustained shifts, spikes (one-time or long term), trends (linear or non-linear), cyclical changes), and may have specific attributes (formal or informal, qualitative or quantitative, verifiable or not, passive or active, timely or delayed, from single or multiple sources, sensitive, geographically specific or widely distributed). Potential signal data are best channeled into a **central database,** monitored by a team that verifies **accuracy** (e.g., OxyContin vs. OxyButynin) and **prioritizes/triages** the information (signal vs. noise); team assessment is relayed to a **multidisciplinary advisory group** with drug safety, epidemiology, regulatory, legal and clinical expertise, that makes decisions on **actionable items** (intervention, further investigation/monitoring).

Interpretation of signals is best done from the perspective of multiple stakeholders seeking a common solution. Signal attributes are used to prioritize/triage incoming data (seriousness of the problem in relation to public safety/health). Multiple signals are integrated and assessed, based on source reliability,

signal types, and decisions about data dissemination. A **"**Levels Framework", where levels are hierarchically organized environments (State, County, community/city, school/peer groups, family, individual) within which abuse occurs, is convenient for cataloguing information and establishing where eventual intervention(s) should be targeted. Three approaches for signal assessment are described. *Rapid Assessments*, completed in ~10 months (ultra-rapid assessments in ~3 weeks), build on existing data to characterize the nature and extent of problems in a specific location. Quantitative surveys, key informant interviews, focus groups, direct observations, intercept interviewing, ethnography, etc., are applied, using a SWAT team approach that employs drug abuse specialists to gather information. A 3-day investigation by Inciardi et al., of an increased street demand for fentanyl patches in Wilmington, DE, revealed abuse by males/females aged 19-51 years, with a history of drug use; opioid procurement via elderly patients, doctor shopping, or out-of-state students; preferential prescribing of fentanyl over other alternatives; and easier access due to leftover medication and lower expense (relative to heroin). Interventions included education of physicians, and of patients in residential health care facilities. *The Field Research Process* gleans patterns from large, product-specific data repositories on abuse and diversion maintained by the sponsor. Field researchers confirm signal indications, then relay data to an inter-departmental group with drug safety, pharmacovigilance and legal expertise. The company responds to actionable assessments by educating patients and prescribers about drug use and safe storage, and/or by mobilizing additional stakeholders. 3) *Post-marketing surveillance* involves review of all data sources (NSDUH, forensic laboratory information systems, FDA adverse effect reports, DAWN Live, etc.), patient interviews upon entry into treatment programs, data from snowball sampling, ethnographic studies to follow up signals, physician surveys, and monitoring of Internet newsgroups (NADDI's Rx News). Advisory groups determine the need for further action. Once a signal is confirmed, staged assessments are used to phase in more intensive procedures, including background examination of media reports and existing data, telephone and in-person interviews with key informants, use of focus groups with patients in treatment programs, observations and intercept interviews, large scale use of rapid assessment, and ongoing ethnographic studies.

III. Interventions. Rational choice of interventions aimed at mitigating risk relies critically on results of detailed risk analyses described above. Clarification of stakeholder roles and responsibilities is important for designing effective approaches. E.g., manufacturers have a clear responsibility for devising product safety-related solutions, using industry-specific tools (product safety inserts), in parallel with education about proper prescribing, use, and dispensing of marketed opioid analgesics, and ways to protect against abuse and diversion. However, signals may transcend individual products, pointing to an underlying public health problem with POA, and may require input from a broader spectrum of stakeholders. The pharmaceutical industry has also responded to the epidemic of POA by developing abuse deterrent formulations (Talwin NX), retraining sales representatives, and introducing restrictions for off-label marketing. Potential interventions with high prescribing clinicians (TIP sheets, Dear Dr. letters, Clinician Report Cards, in-person conversations by Medical Boards or opioid abuse experts), and a role for local and national media are also important for this effort. Prescription monitoring programs at the State level are effective in reducing doctor-shopping. A wider societal responsibility in educating patients and families to secure medication, reduce access, and appropriately dispose unused medication, and in school-based interventions, is strongly endorsed.

IV. Conclusions, Future Directions. Participants presented a rational framework for signal assessment that includes prioritizing and assessing signals, endorsed the development of policies based on collaboration with related stakeholders. Public domain sharing of experience with signal management processes that are already implemented by some companies is essential. The results of the assessments should be matched to an appropriate and cost-effective intervention and much more attention is needed to devising ways for evaluating the outcomes of such interventions.