2nd Tufts Health Care Institute Meeting

Development of Abuse-Resistant Opioid Products

EXECUTIVE SUMMARY

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Notes:
- Recommendations from the meeting are indicated below in **bold**.

"It is tragically ironic that, while our streets are awash in prescription medications, the under-treatment of pain in legitimate patients remains a national problem."

- Senator Susan Collins, Boston Globe, August 8, 2003

Background

Unrelieved pain and prescription opioid abuse are two inextricably interconnected major public health problems in the United States. Initiatives to combat the unrelieved pain problem or the prescription opioid abuse problem can be characterized as either "balanced" or "unbalanced." "Unbalanced" initiatives are those which worsen one problem while addressing the other; for example, restricting opioid access may reduce prescription opioid abuse but will worsen access to opioid therapy for patients who need it. "Balanced" initiatives are those which are expected to simultaneously address both prescription opioid abuse and unrelieved pain. The development and marketing of abuse-resistant prescription opioid products is among the most important balanced risk management approaches available, with the potential to both improve access to pain relievers while decreasing prescription opioid abuse.

Efforts to develop such products have a long and checkered history. The challenges to developing abuse-resistant products are technical, scientific, regulatory, and economic. Development of an abuse-resistant opioid must be justified by potential sales. Sales requires promotion. Promotion is closely regulated by FDA, and must be based on information contained within the product label. Information in the label must be derived from studies conducted according to accepted scientific standards. Also, prescription opioid abuse is not uniform, but consists of a number of different phenomena, which would respond differently to different abuse-resistant approaches, and need to be assessed differently.

Thus successful development of abuse-resistant opioids requires defining the subtypes of prescription opioid abuse, technical product development, accepted scientific methods to measure differences in abuse liability, standards for including the results of such studies in the product label, and standards for promotion of these products based on the product label. The purpose of this meeting was to begin the process of developing these elements of a pathway towards the development of abuse-resistant opioids.

Subtypes of prescription opioid abuse. Several distinct types of prescription opioid abusers can be discerned, including the "hard core" heroin addict, "hard core" prescription drug addict, polydrug abuser, rave abuser, inexperienced abuser, and patient abuser. (See discussion of terminology below.) Different approaches to abuse resistance will be required in different circumstances. For example, approaches that deter intravenous injection will have no impact on the vast majority of prescription opioid abusers who chew or swallow intact their products. The types of abuse easiest to address with abuse-resistant formulations may not be the most important from a public health standpoint. **Research is needed to validate the subtypes of prescription opioid abuse and characterize their phenomenology, and effort needed to develop appropriate terminology.**

Approaches to abuse resistance. Goals of abuse-resistant formulations include (a) Resistant to preparation for IV abuse, (b) Resistant to preparation for nasal abuse, (c) Resistant to converting slow onset formulation to rapid onset, (d) Resistant to accelerated extraction with alcohol, and (e) Resistant to supra-therapeutic exposure

(overdose). A variety of approaches have been tried, including inherently less euphorigenic analgesics, inherent dual mechanism analgesics, antagonist combinations, aversive ingredients, prodrugs, non-injectable/tamperable formulations, smart patient dispensation devices, and depot formulations and devices. One speaker summarized efforts to develop abuse-resistant opioids as follows: "If it were that easy it would have been done already."

Pre-meeting survey of invitees. Respondents distinguished specific types of abuse, types of evidence of abuse-resistance, and types of appropriate promotion. New surveillance systems are perceived as the most important sources of evidence for abuse resistance; clinical trials least. Demonstrating reduction of different types of abuse requires different types of evidence. Any downsides (e.g. safety, efficacy, cost) of abuse-resistant formulations pushes routine clinical utilization towards higher risk situations (higher risk patients, higher risk treatment settings, higher risk environments). Convincing payers would require cost-effectiveness data.

Industry perspective. Industry recognizes the potential value of the abuse-resistant opioid market and considers the development of abuse-resistant opioids "the right and responsible thing to do." Several challenges are recognized as noted above. It will be important to manage the expectations of patients, physicians, payers, and regulators, since no product will be abuse-proof, and no product will relieve the clinician of the responsibility to carefully manage their patients on opioid therapy.

Regulatory Issues

The FDA recognizes the need for the development of abuse-resistant opioid products and would like to encourage their development and clinical utilization in a manner consistent with regulatory obligations. Among those requirements is that the labeling of such products will need to be scientifically accurate and evidence-based. Each statement in a product label must be justified by data and submitted in an NDA/BLA.

There are two types of label claims: *implicit* and *explicit*. *Implicit claims* refer to statements and descriptions that may have some relationship to abuse, but the relationship is unproven or indirect. *Explicit claims* require demonstration of decreased abuse in relation to a relevant comparator in a robust, sufficiently prolonged, and sufficiently extended clinical or epidemiologic study. Studying abuse-resistance claims of any type will require careful evaluation of methods, metrics, and analysis plans, and will require input from all appropriate Agency review staff. This is particularly the case for any explicit claims of abuse resistance, since from the Agency's perspective there is little consensus on the methods for conducting such studies. For that reason the Agency currently finds it difficult to envision how to scientifically support an explicit claim in the Indications section of the label such as "relieves pain and is associated with decreased abuse and diversion." Current Agency thinking is that if even possible, it would require large epidemiologic studies with years of real-world data, and would need to address diversion and abuse in the community, and complications associated with abuse.

In general, factual descriptions of scientific data can be placed in the label, and promotion of factual information contained in the product label is permissible, including factual information about studies that relate to abuse liability. A product is considered misbranded if the "labeling is false or misleading in any particular." Also, promotion beyond the label, such as extrapolations of implicit claims to make explicit claims about abuse or addiction, will not be allowed. The FDA has a number of available regulatory mechanisms for addressing violations of these restrictions, and has applied them to manufacturers of opioid analgesics, including for inappropriate promotional activity related to abuse liability.

Additional regulatory concerns include the requirement that any potential impact of an abuse-resistant formulation on either the safety or the efficacy of the product for the intended population be studied.

A review was conducted of drug abuse statements in product labels using ePDR. No specific statements related to abuse-resistance were identified in labels for opioids (but were identified for other drugs); occasional drug dependence and withdrawal data were identified in opioid labels. Examples of statements related to abuse-resistance were found for Lomotil, Lunesta, Marinol, Strattera, and Amerge. Types of statements included information about the intention of the formulation ("…a subtherapeutic amount of XX is present to discourage deliberate overdosage"); absence of addiction-related AEs ("…diphenoxylate has not produced addiction…"); extractability ("the insolubility of XX in aqueous media precludes intravenous self-administration"); withdrawal symptoms; abuse-related outcomes in high-risk patients; subjective responses in abuse liability studies; and episodes of diversion.

In summary, the FDA would like to encourage the pharmaceutical industry towards the responsible development and marketing of abuse-resistant products. Implicit claims resulting from valid studies potentially related to abuse (such as extractability or euphoria) can potentially be included in the product label, and in promotional materials; however the validity of such claims will require thorough review. Explicit claims are possible but the methodology will require much careful consideration, and the threshold for explicit claims will be much higher. In order to facilitate the process of achieving appropriate labeling claims, **early collaboration with the FDA on a Target Product Profile is *strongly encouraged.***

Assessment of Abuse Liability

Benchtop testing. Tampering, or extractability, may be defined as "manipulating a pharmaceutical dosage form to change its (drug delivery) performance in a way not specified or intended by the manufacturer" (from presentation by P. Goliber, PhD). Tampering is distinguished from abuse in that the latter can occur without manipulation of the dosage form. There are currently no industry standards for the evaluation of tampering/extractability despite the effort of some groups. **More work is urgently needed to develop industry standards around the testing and interpretation of tampering/extractability, including issues around alcohol interactions.**

Abuse liability studies. Testing potentially addictive medications in clinical pharmacology studies has long been part of the evaluation of abuse liability. The goals of such studies are: to provide information for the label, to inform scheduling decisions, and to support public health. One study will not answer all questions due to diversity of patient populations, types of abuse, routes of administration, etc. The value of human abuse liability study results in the label includes: providing relevant information, helping define approved use, potential market advantages, and helping shape the risk management program. The phenomena that can be detected in such studies include: (1) aversive effects, (2) prodrugs, (3) antagonist effects, (4) dose-response of active, and perhaps of antagonist, (5) solubility and absorption. These studies are generally regarded as informative, and while there have been gradual refinements in the methods of abuse liability studies over the past several decades, these studies have important limitations. **Further work is needed to promote the development of improved methods of abuse liability studies, particularly those relevant to pain and prescription opioid abuse.**

Clinical trials. In general clinical trials have not been a source of systematically collected information about abuse liability. Reasons for this include the lack of validated methods, particularly outcome measures relevant to abuse; lack of validated constructs and diagnostic criteria (such as abuse or addiction in a pain patient); and the exclusion from clinical trials of high-risk patients, which results in a low "event rate" in the clinical trial setting. Unfortunately, even where validated methods exist, there are rarely applied in a systematic manner. Abuse-related data from clinical trials is currently passively collected (e.g. spontaneous reports of putatively abuse-related adverse events, loss of drug supply), and interpreted, without any scientific consensus around appropriate methods and interpretation.

Despite these limitations, important information on abuse liability can and should be gathered prospectively during the drug development process. Investigators have shown that events potentially related to abuse or diversion can be prospectively collected and adjudicated. The absence of such findings is also highly informative when captured systematically, and has found its way into product labels. Differences in the incidence of aberrant drug behaviors between high- and low-risk patients can be demonstrated in naturalistic studies. **The group felt that abuse deterrence of a formulation could be demonstrated in a clinical trial of high-risk patients using a time-to-exit approach, with exit criteria based on evidence of abuse.** In addition, methods are emerging to directly assess the "attractiveness" of products to abusers; such methods may have a role in assessing abuse liability in the premarket phase.

Epidemiology. Epidemiologic studies are currently viewed as the gold standard for making explicit claims about the extent to which one product is abused compared to another in the community, the sine qua non of abuse resistance. Unfortunately, no such studies have been published, and there is no consensus about accepted methods for conducting or interpreting such studies. Further work is needed to determine the goals, methods, and interpretation of such studies, and their labeling implications.

Surveillance may be defined as "the ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in the planning, implementation, and evaluation of public health practice" (Centers for Disease Control and Prevention). Although there are a plethora of databases and surveillance systems in place for drug abuse, and for prescriptions in general, no surveillance systems exist that provide scientifically valid and

timely estimates of abuse rates of specific products, in a manner that is useful for public health surveillance. **The development of such surveillance methods is necessary to achieve the public health goals of reducing under-treated pain and reducing prescription opioid abuse.**

Terminology

The group recognized that standardization of terminology is a necessary early step towards progress in science and terminology in this area. The group proposed the following terminology, which replicates accepted definitions when such is available.

Abuse: Any use of an illegal drug, or the intentional self-administration of a medication for a non-medical purpose such as altering one's state of consciousness.

Misuse: This term is used in a multitude of ways. One common definition is: "the use of a medication other than as directed." More precise usages distinguish misuse from abuse, by defining misuse as excluding the context of abuse or addiction. Misuse can be defined as either willful or unintentional. Some prefer to specify that the behavior leads to an appreciable negative consequence in order to be considered misuse.

Physical Dependence: A state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance: A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time, or an increase in dose needed to maintain the same effect.

Addiction: A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use; compulsive use; continued use despite harm; and craving.

Pseudoaddiction: A syndrome of behavior resulting from under-treatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior (abuse or addiction), and characterized by cessation of such behaviors once adequate pain relief is provided. This is not a diagnosis, rather a description of a clinical interaction.

Diversion: The intentional removal of a medication from legitimate distribution and dispensing channels.
Abuse Resistant: The group preferred the term **"abuse deterrent,"** because the term "abuse resistant" was felt to imply something approaching "abuse proof," and expectations would be more appropriate under the term "abuse deterrent." An *abuse-deterrent* product is one that is significantly less prone to be "abused" than an appropriate referent product.

Clinical Utilization

The group shared the vision that ultimately all prescription opioids would be abuse-deterrent, but recognized obstacles in realizing that vision. In the case of products that have no new safety or efficacy issues, ideally this medication would be prescribed routinely to all patients. Reimbursement will be a significant issue since abuse-deterrent opioids are likely to be more expensive than generic opioids. Given that cost effectiveness has not been fully considered, a stratified approach in which only high-risk patients are routinely prescribed abuse deterrent agents may be appropriate at present. In reality, new abuse deterrent agents may have either safety or efficacy concerns beyond those of the opioid analgesics they are meant to replace. The need to provide adequate pain relief must be maintained as the primary principle of analgesic therapy. However, it must be recognized that in high-risk patients, the need to prevent the serious complications of abuse and addiction may in many cases outweigh an additional safety burden imposed by an abuse-deterrent product. Prescribing decisions will depend on the detailed properties of the product and the specific patient situation. The position that no safety cost of abuse deterrence is acceptable will frequently not be in the patient's interest.