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医療用麻薬の乱用防止製剤について

医薬行政の推進につきましては、平素より格別の御高配を賜り厚く御礼申し上げます。

医療用麻薬は患者の疼痛緩和等に有益である一方で、乱用による公衆衛生上の危険を生じるおそれがあり、特に米国においては医療用麻薬の乱用が大きな問題となっており、様々な対策が講じられています。我が国においても、非がん疼痛への適用拡大や在宅医療推進等を背景に、医療用麻薬の利用拡大が見込まれる状況を踏まえ、乱用防止対策を推進することが極めて重要となります。

医療用麻薬の乱用防止対策の一つとして、米国では、乱用を防止するための特性を有する製剤（以下「乱用防止製剤」という。）の開発が行われており、錠剤に不正な剤型変更を防止する特性等を付与することにより、乱用を防止することが期待されています（参考１及び２参照)。我が国においても、昨年、乱用防止製剤の承認があったところですが、今後乱用防止製剤を製造する技術の開発やそうした技術を用いた製剤の普及が、乱用防止対策の推進において更に有益と考えられます。

つきましては、医療用麻薬の乱用防止対策の重要性及び乱用防止製剤の意義について、貴管下の医療機関、薬局及び医薬品製造販売業者への周知をお願いいたします。併せて、医療機関及び薬局に対し、乱用防止製剤の使用に向けた検討を行っていただくよう、周知をお願いいたします。

また、医薬品製造販売業者に対し、乱用防止製剤を製造する技術の開発及び臨床におけるニーズに応じた製剤の改良に向けた検討を行っていただくよう、

併せて指導をお願いいたします。なお、乱用防止製剤の開発に関する相談は、当分の間、当局監視指導・麻薬対策課宛てに申し入れていただくよう、周知をお願いいたします。

（参考１）米国における乱用防止製剤の状況

米国内における医療用麻薬等の医療用オピオイド系鎮痛剤の乱用状況から、大統領行政府は、2011 年に医療用オピオイド系鎮痛剤の乱用防止対策として、米国食品医薬品局（FDA）に対し乱用防止製剤の開発等に関する製薬企業向けガイダンスを作成するよう指示した（別添１）。FDA は 2015 年に乱用防止製剤に関する製薬企業向けガイダンス（別添２）を公表し、当該ガイダンスにおいて乱用防止製剤の開発を公衆衛生上の優先順位が高いものと位置づけた。なお、米国では既に複数の乱用防止製剤が承認されている。

（参考２）米国において乱用防止製剤に用いられている特性の例

・物理的抵抗性の付与

製剤のかみ砕き、押し潰し、切断、すり潰し、粉砕を防止するもの。

・化学的抵抗性の付与

ゲル化等により、水等の溶媒による麻薬成分の抽出を防止するもの。

・有効成分に対する拮抗成分の配合

拮抗薬の添加により、多幸感など乱用の目的となる効果を妨げ、減少し、又は打ち消すもの。

（参考資料）

・別添１　「EPIDEMIC: RESPONING TO AMERICA’S PRESCRIPTION DRUG ABUSE CRISIS」（抄）（2011 年、米国大統領行政府公表）

・別添２　「Abuse-Deterrent Opioids-Evaluation and Labeling Guidance for Industry」（抄）（2015 年、米国食品医薬品局（FDA）公表）

EPIDEMIC: RESPONDING TO AMERICA'S PRESCRIPTION DRUG ABUSE CRISIS

2011

EXECUTIVE OFFICE OF THE PRESIDENT OF THE UNITED STATES
OFFICE OF NATIONAL DRUG CONTROL POLICY

Background

Prescription drug abuse is the Nation's fastest-growing drug problem. While there has been a marked decrease in the use of some illegal drugs like cocaine, data from the National Survey on Drug Use and Health (NSDUH) show that nearly one-third of people aged 12 and over who used drugs for the first time in 2009 began by using a prescription drug non-medically.[1] The same survey found that over 70 percent of people who abused prescription pain relievers got them from friends or relatives, while approximately 5 percent got them from a drug dealer or from the Internet.[2] Additionally, the latest Monitoring the Future study—the Nation's largest survey of drug use among young people—showed that prescription drugs are the second most-abused category of drugs after marijuana.[3] In our military, illicit drug use increased from 5 percent to 12 percent among active duty service members over a three-year period from 2005 to 2008, primarily attributed to prescription drug abuse.[4]

Although a number of classes of prescription drugs are currently being abused, this action plan primarily focuses on the growing and often deadly problem of prescription opioid abuse. The number of prescriptions filled for opioid pain relievers—some of the most powerful medications available—has increased dramatically in recent years. From 1997 to 2007, the milligram per person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams, an increase of 402 percent.[5] In addition, in 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48 percent.[6] Further, opiate overdoses, once almost always due to heroin use, are now increasingly due to abuse of prescription painkillers.[7]

These data offer a compelling description of the extent to which the prescription drug abuse problem in America has grown over the last decade, and should serve to highlight the critical role parents, patients, healthcare providers, and manufacturers play in preventing prescription drug abuse.

These realities demand action, but any policy response must be approached thoughtfully, while acknowledging budgetary constraints at the state and Federal levels. The potent medications science has developed have great potential for relieving suffering, as well as great potential for abuse. There are many examples: acute medical pain treatment and humane hospice care for cancer patients would be impossible without prescription opioids; benzodiazepines are the bridge for many people with serious anxiety disorders to begin the process of overcoming their fears; and stimulants have a range of valuable uses across medical fields. Accordingly, any policy in this area must strike a balance between our desire

1. *Results from the 2009 National Survey on Drug Use and Health (NSDUH): National Findings*, SAMHSA (2010).
2. *Results from the 2009 National Survey on Drug Use and Health (NSDUH): National Findings*, SAMHSA (2010).
3. University of Michigan, 2009 Monitoring the Future: *A Synopsis of the 2009 Results of Trends in Teen Use of Illicit Drugs and Alcohol.*
4. *2008 Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel*, Department of Defense (2009). Available at: http://www.tricare.mil/2008HealthBehaviors.pdf
5. Manchikanti L, Fellow B, Ailinani H, Pampati V. Therapeutic Use, Abuse, and Nonmedical Use of Opioids: A Ten-Year Perspective. *Pain Physician*. 13:401-435. 2010.
6. Based on data from SDI, Vector One: National. Years 2000-2009. Extracted June 2010. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM217510.pdf
7. *Unintentional Drug Poisoning in the United States*, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, July 2010.

to minimize abuse of prescription drugs and the need to ensure access for their legitimate use. Further, expanding effective drug abuse treatment is critical to reducing prescription drug abuse, as only a small fraction of drug users are currently undergoing treatment.

This Prescription Drug Abuse Prevention Plan expands upon the Administration's *National Drug Control Strategy* and includes action in four major areas to reduce prescription drug abuse: education, monitoring, proper disposal, and enforcement. First, education is critical for the public and for healthcare providers to increase awareness about the dangers of prescription drug abuse, and about ways to appropriately dispense, store, and dispose of controlled substance medications. Second, enhancement and increased utilization of prescription drug monitoring programs will help to identify "doctor shoppers" and detect therapeutic duplication and drug-drug interactions. Third, the development of consumer-friendly and environmentally-responsible prescription drug disposal programs may help to limit the diversion of drugs, as most non-medical users appear to be getting the drugs from family and friends. Fourth, it is important to provide law enforcement agencies with support and the tools they need to expand their efforts to shut down "pill mills" and to stop "doctor shoppers" who contribute to prescription drug trafficking.

I. Education

A crucial first step in tackling the problem of prescription drug abuse is to raise awareness through the education of parents, youth, patients, and healthcare providers. Although there have been great strides in raising awareness about the dangers of using illegal drugs, many people are still not aware that the misuse or abuse of prescription drugs can be as dangerous as the use of illegal drugs, leading to addiction and even death.

Parents and youth in particular need to be better educated about the dangers of the misuse and abuse of prescription drugs. There is a common misperception among many parents and youth that prescription drugs are less dangerous when abused than illegal drugs because they are FDA-approved. Many well-meaning parents do not understand the risks associated with giving prescribed medication to a teenager or another family member for whom the medication was not prescribed. Many parents are also not aware that youth are abusing prescription drugs; thus, they frequently leave unused prescription drugs in open medicine cabinets while making sure to lock their liquor cabinets. These misperceptions, coupled with increased direct-to-consumer advertising, which may also contribute to increased demand for medications,[8,9] makes effective educational programs even more vital to combating prescription drug abuse.

In addition, prescribers and dispensers, including physicians, physicians assistants, nurse practitioners, pharmacists, nurses, prescribing psychologists, and dentists, all have a role to play in reducing prescription drug misuse and abuse. Most receive little training on the importance of appropriate prescribing and dispensing of opioids to prevent adverse effects, diversion, and addiction. Outside of specialty addiction treatment programs, most healthcare providers have received minimal training in how to

8. Frosch DL, Grande D, Tarn DM, Kravitz RL. A decade of controversy: balancing policy with evidence in the regulation of prescription drug advertising. *Am J Public Health*. 2010;100(1):24-32.

9. Greene JA, Kesselheim AS. Pharmaceutical marketing and the new social media. *N Engl J Med*. 2010;363(22):2087-2089.

recognize substance abuse in their patients. Most medical, dental, pharmacy, and other health professional schools do not provide in-depth training on substance abuse; often, substance abuse education is limited to classroom or clinical electives. Moreover, students in these schools may only receive limited training on treating pain.

A national survey of medical residency programs in 2000 found that, of the programs studied, only 56 percent required substance use disorder training, and the number of curricular hours in the required programs varied between 3 to 12 hours.[10] A 2008 follow-up survey found that some progress has been made to improve medical school, residency, and post-residency substance abuse education; however, these efforts have not been uniformly applied in all residency programs or medical schools.[11]

Educating prescribers on substance abuse is critically important, because even brief interventions by primary care providers have proven effective in reducing or eliminating substance abuse in people who abuse drugs but are not yet addicted to them. In addition, educating healthcare providers about prescription drug abuse will promote awareness of this growing problem among prescribers so they will not over-prescribe the medication necessary to treat minor conditions. This, in turn, will reduce the amount of unused medication sitting in medicine cabinets in homes across the country.

The following action items will be taken to improve educational efforts and to increase research and development:

Healthcare Provider Education:

- Work with Congress to amend Federal law to require practitioners (such as physicians, dentists, and others authorized to prescribe) who request DEA registration to prescribe controlled substances to be trained on responsible opioid prescribing practices as a precondition of registration. This training would include assessing and addressing signs of abuse and/or dependence. (**ONDCP**/**FDA**/DEA/SAMHSA)
- Require drug manufacturers, through the Opioid Risk Evaluation and Mitigation Strategy (REMS), to develop effective educational materials and initiatives to train practitioners on the appropriate use of opioid pain relievers. (**FDA**/ONDCP/SAMHSA)
- Federal agencies that support their own healthcare systems will increase continuing education for their practitioners and other healthcare providers on proper prescribing and disposal of prescription drugs. (**VA**/HHS/**IHS**/**DOD**/**BOP**)
- Work with appropriate medical and healthcare boards to encourage them to require education curricula in health professional schools (medical, nursing, pharmacy, and dental) and continuing education programs to include instruction on the safe and appropriate use of opioids to treat pain while minimizing the risk of addiction and substance abuse. Additionally, work with relevant medical, nursing, dental, and pharmacy student groups to help disseminate educational materials, and establish student programs that can give community educational presentations

10. Isaacson JH, Fleming M, Kraus M, Kahn R, Mundt M. A National Survey of Training in Substance Use Disorders in Residency Programs. *J Stud Alcohol*. 61(6):912-915. 2000.

11. Polydorou S, Gunderson EW, Levin FR. Training Physicians to Treat Substance Use Disorders. *Curr Psychiatry Rep*. 10(5):399-404. 2008.

on prescription drug abuse and substance abuse. (HHS/**SAMHSA**/**ONDCP**/FDA/HRSA/NIDA/DOD/VA)

- In consultation with medical specialty organizations, develop methods of assessing the adequacy and effectiveness of pain treatment in patients and in patient populations, to better inform the appropriate use of opioid pain medications. (HHS/**CDC**/**SAMHSA**/FDA)
- Work with the American College of Emergency Physicians to develop evidence-based clinical guidelines that establish best practices for opioid prescribing in the Emergency Department. (**CDC**/FDA/ONDCP/NIDA/SAMHSA/CMS)
- Work with all stakeholders to develop tools to facilitate appropriate opioid prescribing, including development of Patient-Provider Agreements and guidelines. (HHS/**FDA**/SAMHSA/NIDA)

Parent, Youth, and Patient Education:

- Enlist all stakeholders to support and promote an evidence-based public education campaign on the appropriate use, secure storage, and disposal of prescription drugs, especially controlled substances. Engage local anti-drug coalitions, and other organizations (chain pharmacies, community pharmacies, boards of pharmacies, boards of medicine) to promote and disseminate public education materials and to increase awareness of prescription drug misuse and abuse. (**ONDCP**/CDC/FDA/DEA/IHS/ED/SAMHSA/DOD/VA/EPA)
- Require manufacturers, through the Opioid Risk Evaluation and Mitigation Strategy (REMS), to develop effective educational materials for patients on the appropriate use and disposal of opioid pain relievers. (**FDA**/ONDCP/SAMHSA)
- Working with private-sector groups, develop an evidence-based media campaign on prescription drug abuse, targeted to parents, in an effort to educate them about the risks associated with prescription drug abuse and the importance of secure storage and proper disposal of prescription drugs (including through public alerts or other approaches to capture the attention of busy parents). (**ONDCP**/ONC)

Research and Development:

- Expedite research, through grants, partnerships with academic institutions, and priority New Drug Application review by FDA, on the development of treatments for pain with no abuse potential as well as on the development of abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential. (**NIDA**/**FDA**)
- Continue advancing the design and evaluation of epidemiological studies to address changing patterns of abuse. (**CDC**/FDA/NIDA)
- Provide guidance to the pharmaceutical industry on the development of abuse-deterrent drug formulations and on post-market assessment of their performance. (**FDA**)

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Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical
April 2015

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Contains Nonbinding Recommendations

Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. The guidance makes recommendations about how those studies should be performed and evaluated and discusses how to describe those studies and their implications in product labeling.

This guidance is intended to assist sponsors who wish to develop opioid drug products with potentially abuse-deterrent properties and is not intended to apply to products that are not opioids or opioid products that do not have the potential for abuse.

This guidance also does not address issues associated with the development or testing of generic formulations of abuse-deterrent opioid products. FDA intends to address that topic in one or more future guidance documents.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Prescription opioid products are an important component of modern pain management. However, abuse and misuse of these products have created a serious and growing public health problem. One potentially important step towards the goal of creating safer opioid analgesics has

[1] This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products, the Office of Regulatory Policy, the Office of Surveillance and Epidemiology, the Office of Biostatistics, and the Controlled Substance Staff in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

been the development of opioids that are formulated to deter abuse. FDA considers the development of these products a high public health priority.

Because opioid products are often manipulated for purposes of abuse by different routes of administration or to defeat extended-release (ER) properties, most abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding. It should be noted that these technologies have not yet proven successful at deterring the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria. Moreover, the fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there may always be some abuse of these products.

For purposes of this guidance, *abuse-deterrent properties* are defined as those properties shown to meaningfully ***deter*** abuse, even if they do not fully ***prevent*** abuse. The term *abuse* is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.[2] Abuse is not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[3] This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.[4]

The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Based on the evolving nature of the field, FDA intends to take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products. Methods for evaluating the abuse-deterrent properties of new molecular entities may have to be adapted based on the characteristics of those products and the anticipated routes of abuse. The development of an abuse-deterrent opioid product should be guided by the need to reduce the abuse known or expected to occur with similar products.

Because FDA expects that the market will foster iterative improvements in products with abuse-deterrent properties, no absolute magnitude of effect can be set for establishing abuse-deterrent characteristics. As a result, FDA intends to consider the *totality of the evidence* when reviewing the results of studies evaluating the abuse-deterrent properties of a product.

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[2] Smith S M, Dart R C, Katz N P, et al. 2013. Classification and definition of misuse, abuse, and related events in clinical trials: ACTTION systematic review and recommendations. *Pain*, 154:2287-2296.

[3] Ibid.

[4] FDA's current Good Manufacturing Practice regulations include tamper-evident packaging requirements. See 21 CFR 211.132. There are also requirements for child resistant "special packaging" under the Poison Prevention Packaging Act and regulations adopted by the Consumer Protect Safety Commissioner (CPSC) in 16 CFR 1700.

As with all NDA products, FDA intends to consider opioids with abuse-deterrent properties within the context of available therapy. The standard against which each product's abuse-deterrent properties are evaluated will depend on the range of abuse-deterrent and non-abuse-deterrent products on the market at the time of that application.[5]

Abuse-deterrent properties can generally be established only through comparison to another product.

FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.

FDA believes it is critical to address the problem of opioid abuse while seeking to ensure that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care and with difficulty swallowing may need access to opioid products that are in solution or that can be crushed.

The following section describes the categories of abuse-deterrent products. The premarket and postmarket studies that should be performed to assess the impact of a potentially abuse-deterrent product are discussed in subsequent sections. Finally, information is provided about labeling for abuse-deterrent products.

III. ABUSE-DETERRENT PRODUCTS

Opioid products can be abused in a number of ways. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product. As a general framework, abuse-deterrent formulations can currently be categorized as follows:

1. *Physical/chemical barriers* – Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.
2. *Agonist/antagonist combinations* – An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be

[5] For guidance on the evaluation of abuse potential for purposes of the Controlled Substances Act (CSA), we refer sponsors to FDA's draft guidance for industry *Assessment of Abuse Potential of Drugs*. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf. FDA guidances are available at http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

3. *Aversion* – Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.
4. *Delivery System* (including use of depot injectable formulations and implants) – Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.
5. *New molecular entities and prodrugs*– The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).
6. *Combination* – Two or more of the above methods could be combined to deter abuse.
7. *Novel approaches* – This category encompasses novel approaches or technologies that are not captured in the previous categories.

IV. PREMARKET STUDIES

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls[6] and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

The evaluation of an abuse-deterrent formulation should take into consideration the known routes of abuse for the non-abuse-deterrent predecessor or similar products, as well as anticipate the effect that deterring abuse by one route may have on shifting abuse to other, possibly riskier route. For example, if a product is known to be abused using nasal and intravenous routes, developing deterrent properties for the nasal route in the absence of deterrent properties for the intravenous route risks shifting abusers from the nasal to the intravenous route, which is associated with a greater risk for the spread of infectious diseases.

Another concept that should be considered is whether the deterrent effects can be expected to have a meaningful impact on the overall abuse of the product. For example, immediate-release (IR) opioid and acetaminophen combination products are predominantly abused using the oral

[6] For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.

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