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Division of Dockets Management

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Food and Drug Administration

5630 Fishers Lane, Room 1061

Rockville, MD 20852

www.regulations.gov

Re: Docket No. 2009-N-0143: Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting

These comments are submitted in response to the April 20, 2009, Federal Register Notice requesting comments on the proposed Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs [**Federal Register Meeting Notice: Docket No. FDA-2009-N-0143**, CDER 200914. Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting. Pages 17967-17970 [FR Doc. E9-8992]].

Pinney Associates appreciates the opportunity to comment directly to the Food and Drug Administration (FDA) on the proposed REMS for long-acting and extended-release opioids. Pinney Associates' scientists and health policy experts provide science and public health based strategic solutions to support decision making among pharmaceutical companies, including premarketing risk assessments, data collection and analysis, and the development and implementation of risk management programs and REMS.

These comments aim to 1) review key points made in our presentation at the public meeting on May 27-28 (Sidney H. Schnoll, M.D., Ph.D., *REMS: Intended Purpose and Unintended Consequences*), 2) answer questions raised by the agency after that presentation, and 3) provide comments on the large amount of information and many recommendations presented at the meeting. Our comments are also intended to give an informed broad perspective on the historical context of the problem of prescription drug abuse, propose a rationale strategic approach, suggest desired outcomes, and outline potential challenges presented by implementation of the proposed class-wide REMS for long-acting and extended-release opioids.

3 Bethesda Metro Center, Suite 1400, Bethesda, MD 20814

301-718-8440/0034 FAX

1 Public Health Challenge

We would like to first review relevant history, identify some key public health challenges, provide some thoughts on the proposed compassionate use and review the scope of the proposed class-wide REMS.

1.1 Recent History of Opioid Abuse and Efforts to Address Abuse

Prescription drug abuse in the United States (U.S.) is not a new problem. It has been around and acknowledged for over a century, and there have long been legislative efforts at the federal, state and local level to curtail prescription drug abuse in the U.S., but even so, prescription drug abuse is rising. The primary focus of these efforts has been to address the supply of drugs available for abuse.

It is commonly believed that one of the first major peaks of abuse of prescription drugs followed the U.S. Civil War when many veterans were dependent on the morphine used to treat the pain associated with their war injuries, although this thesis has been questioned in recent decades as to whether or not this problem actually existed.^{1,2,3}

As early as 1875, policy makers addressed drug abuse with laws passed to control abuse of a variety of drugs with abuse potential, beginning with opium and its derivatives (San Francisco Anti-Opium Law of 1875; Virginia City Anti-Opium Law 1876). Throughout the 20th century, policy makers continued to try to address the problem of prescription drug abuse through national and local legislation. The Pure Food and Drug Act of 1906, which was intended to reduce the abuse of patent medicines, required that the label on those medicines include all ingredients. At that time, patent medicines often contained combinations of tincture of opium and cocaine dissolved in alcohol. Also in 1906, the District of Columbia Pharmacy Act required a physician's prescription for products containing opium, cocaine, or chloral hydrate. Further, the act allowed physicians to prescribe narcotics to addicts only if it was "necessary for the cure" of addiction. In 1914, the Harrison Narcotics Act first taxed and placed limits on the importation of morphine and cocaine-based products. Several legal cases in the early 1920s highlighted a lack of clarity about for whom these medications could be prescribed and whether or not physicians could legally treat addicts with opiate medication.

The Marijuana Tax Act of 1937 removed tincture of cannabis from the U.S. Pharmacopeia. More recently, the Controlled Substances Act of 1970 established the

¹ Courtwright D. Dark Paradise: A History of Opiate Addiction in America. Cambridge: Harvard University Press;1982:16-28.

² Musto D. The American Disease. New Haven: Yale University Press; 1973:2-4.

³ Mandel J. The mythical roots of U.S. drug policy: soldier's disease and addiction in the Civil War. Journal of Civil War medicine. 1999 Jul-Sept; 3(3):71-84. Available at: <http://www.druglibrary.org/schaffer/History/soldis.htm>

five schedules in which U.S. agencies place most drugs with abuse potential. It is important to note that these laws, all intended to control and reduce the abuse and diversion of prescription and illicit drugs, have met with varying degrees of success.

Despite the enactment of laws aimed at reducing the abuse of prescription medicines, data suggests that in recent years there has been a large increase in the nonmedical use of these medications, especially pain relievers with abuse potential. While the data suggest this increase started in the early 1990s, it should be noted that few data on nonmedical prescription drug use were collected prior to that time. Most of the data collected before the early 1990s addressed illicit drug use. In recent years, in response to the rise in the nonmedical use of prescription drugs, the U.S. government has granted FDA the authority to take important steps to address the problem, and FDA has and continues to act to do so.

1.2 FDA Proposal: Long-Acting and Extended-Release Opioid REMS

The Food and Drug Administration Amendments Act of 2007 (FDAAA) for the first time gave FDA authority to require pharmaceutical companies to minimize the risks associated with a medication while maintaining the medication's benefits. As applied, these risks include abuse, misuse, overdose and addiction. More specifically, FDAAA gave FDA authority to require sponsors to implement a Risk Evaluation and Mitigation Strategy (REMS) to manage a known or potential serious risk to ensure that the benefits of a medication outweigh its risks. FDAAA identifies potential REMS tools to address risks, including for example, education, such as letters to prescribers reminding them of certain safety precautions and Medication Guides, special certification of prescribers, limits on dispensing to certain pharmacies, or requiring prescribers or patients to enroll in a registry.

FDA's recent call for a single, class-wide REMS to be applied to all extended-release and long-acting opioids, both branded and generic, is an important first step to apply the REMS legislation consistently to this class of medications. The public health issue created by the inappropriate use of long-acting and extended-release opioids, whether intentional or accidental, is a widespread problem in the U.S. contributed to by a multitude of factors. While the proposed REMS has the potential to have a real impact on the problem of non-medical opioid use, there are a series of challenges FDA must address as it finalizes the proposed REMS if the REMS is to have the intended impact on nonmedical use without having unintended impacts on the care of pain patients who need these medications.

1.3 Public Health Challenges Posed by the Proposed Long-Acting and Extended-Release Opioid REMS

The proposed long-acting and extended-release opioid REMS poses challenges distinct from existing REMS that FDA and other stakeholders will need to consider as the proposed REMS is developed and implemented. Some of these challenges include:

- The opioid REMS will increase the stigma associated with use of opioid pain medications, making pain patients more reluctant to take the medications they

need to control chronic pain. Care should be taken that the REMS does not reinforce the perceived stigma of opioid use.

- Other REMS already implemented are either very basic REMS (e.g., antiepileptic medications have just a Medication Guide), or have a complexity comparable to the proposed opioid REMS but apply to single products (e.g., Tysabri) or single active ingredients (e.g., isotretinoin). In contrast, the highly complex opioid REMS as proposed would include seven individual active ingredients that are included in products produced by more than 25 manufacturers, and used for two indications.
- The multiple products included in the proposed REMS represent a range of pharmacological properties and formula-specific considerations.
- Most REMS to this date have been primarily designed to address risks in the patient population for which the medication is prescribed, because abuse and diversion by others were not of major concern.
- The main focus of the proposed opioid REMS is to ensure the medications are used as prescribed in the appropriate patient population. A variety of controls on access to opioids are already in place (i.e., scheduling, tamper resistant prescription pads, requirements for dispensing, etc). While these controls are intended to reduce access to those who may divert and/or abuse the drug, they were not intended to make access unduly difficult for pain patients in need of these medications.
- The REMS for long-acting and extended-release opioids is intended to provide protections for legitimate patients (e.g., from unintentional overdose), but also to carry the additional burden of impacting the growing problem of prescription drug abuse.
- Other REMS require measurement of outcomes (e.g., pregnancy) only among the patient population; with the long-acting and extended-release opioid REMS there will be the need to measure and monitor multiple adverse outcomes among both patients and the U.S. population. The definition of a positive outcome, especially for the U.S. population metrics, is somewhat unclear. Experience in specific geographic areas of the U.S. suggests that reducing the prevalence of one outcome (e.g., addiction) can have paradoxical consequences by increasing the incidence of other outcomes (e.g., overdose), as noted in the REMS docket submission from The Chronic Pain Initiative and Project Lazarus, Wilkes County, North Carolina.
- There are strong genetic and social influences involved in the abuse of, and addiction to, drugs that are beyond the control of any REMS but critically influential in determining its success.

We believe it is preliminary to include the immediate-release opioids in a REMS at this point. The complexities of integrating the number of prescribers and patients for

extended-release and long-acting opioids alone are magnitudes larger relative to existing REMS. For example, in 2008 there were 20,000 isotretinoin prescribers and roughly 1 million prescriptions filled under the iPledge program. In contrast, there were 375,000 prescribers of extended-release opioids and 26 million prescriptions filled. A REMS for *all* opioids would encompass approximately 200 million prescriptions per year.

1.4 Need to Address Supply and Demand

As described above (see section 1.1), more than a century of laws have been passed to control abuse of drugs by attempting to limit supply. The continued abuse and diversion of prescription drugs from legitimate sources demonstrates the failure of these supply side approaches. Decades of research from the National Institute on Drug Abuse has consistently demonstrated that the most effective approaches to the treatment of drug abuse include a balance of efforts between supply and demand reductions. Any REMS designed to reduce the supply of prescription drugs for abuse and diversion can only be successful if there is a parallel effort to augment prevention and treatment programs to reduce demand. Another supply side only approach will result in a failure to curb abuse and overdose while reducing the availability of medications for patients who need them.

1.5 Need to Consider Potential Impact of Compassionate Use

One proposal presented at the May 27-28, 2009 public meeting on the long-acting and extended-release opioid REMS involved the immediate restriction of all long-acting opioids to use only in patients with cancer pain, and a compassionate use policy for those with non-cancer pain. Thirty million people in the U.S. live with or are in remission from cancer⁴, making a cancer-only indication very difficult to implement and monitor in practice. This type of program would raise a number of challenging decisions, for example:

- If an individual has a malignancy in remission and the emergent pain is at a different site, would the patient be a candidate under the compassionate use policy or under a previous authorization for the cancer pain?
- With a high burden of non-malignant skin cancer, would anyone with a history of a skin cancer diagnosis be eligible?
- If the decision is left to the physician, whether the pain is associated with a malignancy or not, primary care doctors may be unreasonably burdened with trying to distinguish between sites of origin for a spreading cancer and from where the pain is originating.
- How would a compassionate use program impact coverage by insurance companies, pharmacy benefits managers, and public assistance sources?

⁴ Jemal A, Thun MJ, Ries LA, Howe HL, Weir HK, Center MM, Ward E, Wu XC, Ehemann C, Anderson R, Ajani UA, Kohler B, Edwards BK. Annual report to the nation on the status of cancer, 1975-2005, featuring trends in lung cancer, tobacco use, and tobacco control. J Natl Cancer Inst. 2008 Dec 3;100(23):1672-94.

- Studies estimate that approximately 50 million Americans suffer from chronic non-cancer related pain at some time in their lives. The healthcare burden on making rigorous clinical assessments is enormous and would most likely result in litigation for those denied access. For patients with non-cancer related pain, who would make the decision as to whether or not they should fall under a compassionate use program? Would this decision be made by their prescriber? What would be the role of the coverage provider?

From a data analysis perspective, these problems would be particularly manifest when using claims data from third party payers (e.g., insurance companies, pharmacy benefits managers and public assistance sources) to understand the impact of the compassionate use program on patient care and access.

Before the agency considers a compassionate use proposal in earnest, there are two specific “natural experiments” which ought to be evaluated to understand the impact such a policy would have.

- The breakthrough cancer pain indication for Fentora[®] means that insurance companies and pharmacy benefits managers often will not pay for this relatively expensive medication in patients with non-cancer pain. How this has affected patient care and access was discussed during the May 6, 2008 meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The onus for proving the need for this medication for non-cancer breakthrough pain is on the provider and patient, paralleling the “compassionate use” proposal. Despite the significant burden on patients and the generally adversarial payer system, most of the use of this product is for non-cancer pain. This experience suggests that the proposed “compassionate use” concept would have limited effectiveness in limiting the use of extended-release and long-acting opioids to cancer pain.
- The second source of natural experiments comes from state Medicaid programs and pharmacy benefits payers. Prior authorization and other formulary-based requirements for branded opioids have been instituted in many programs to constrain the financial costs associated with these medications. For example, starting in the summer of 2008, North Carolina’s Medicaid program required beneficiaries first to attempt chronic pain control using generic extended-release morphine for 30 days, before the program paid for any other Schedule II extended-release (e.g., branded) opioids. The evaluation for the effects of this rule provides a case study of the multi-faceted approach that must be taken. For example, the number of patients being switched to methadone was monitored, as well as the use of other opioids outside of the prior authorization and overdose deaths and claims among beneficiaries. The financial costs and savings associated with the policy change were also quantified. One particularly enlightening approach was to evaluate changes over time not only to the number of prescriptions that were paid for, but also the number of claims and the number of unique beneficiaries. When used in tandem, these metrics provided a comprehensive assessment of the effects of the policy change with confidence in

the findings. Changes in prescribing were evident, and although there wasn't a major increase in the number of patients receiving analgesic methadone, the overdose rates among beneficiaries continued to increase. The evaluation provides one model for evaluation and shows the folly of relying solely on supply side reduction.

We do not support the compassionate use proposal; however, if FDA considers including a compassionate use policy in the proposed REMS, research must be done to understand what the potential impact, including the potential unintended impact, of such a policy might be.

1.6 Scope of the Public Health Challenges

The development and implementation of the proposed REMS will be a gargantuan task for all stakeholders. The potential consequences, both intended and unintended, must be considered at each step. It will be critical to take lessons learned from the existing REMS regardless of the differences in both scope and magnitude to the proposed long-acting and extended-release opioid REMS. The success of the proposed REMS will require both providers and patients to take accountability. It will require buy-in and cooperation from many levels and functions of government, industry, science, and the healthcare communities. A cohesive relationship between these and other stakeholders for the proposed REMS must be created and maintained, despite competing interests. There are time and economic factors that must be planned for and controlled. While there is no easy way to implement a program that can cover all aspects of abuse, addiction, misuse and overdose, it is imperative that thought is given to the public health considerations with the appropriate focus on both the intended population for these medications and the populations of unintended users.

2 Process

Based on our experience and expertise, we have several key recommendations to make with regard to next steps. These include the need for all key stakeholders to work collaboratively, the need for an appropriate pilot and our agreement that methadone offers an advantage for the pilot and a brief statement regarding timing and reporting.

2.1 Importance of Stakeholder Involvement

We applaud FDA's efforts to obtain input from multiple stakeholders through meetings including the February 10, 2009 meeting with other governmental agencies and patient representatives; the March 3, 2009 meeting with the companies that market extended-release opioids; the May 4 and 5, 2009 meetings with stakeholders other than the pharmaceutical industry; and the May 27 and 28, 2009 public meeting. These meetings were important first steps in an ongoing process to provide effective REMS for these products. We would, however, strongly encourage FDA to provide further opportunities for these key stakeholders to come together as a group to work collaboratively to address challenges raised by the development and implementation of the proposed REMS.

As a next step, we urge FDA to take the lead in establishing such opportunities for all the key stakeholders to work in concert together. This should include decision-makers

in industry; health care professional groups representing doctors, nurses/nurse practitioners, physicians assistants, podiatrists, dentists, hospice care providers, hospital practitioners, pharmacists, and substance abuse treatment providers; insurance companies; patients and caregivers; drug dependence researchers; federal agencies (including FDA, the Drug Enforcement Administration (DEA), Substance Abuse and Mental Health Services Administration (SAMHSA), Office of National Drug Control Policy (ONDCP), and NIDA); and both proprietary and governmental data owners. Given the scope of the REMS program being designed, long-term commitments and effort from all stakeholders will be required if the REMS is to be effective.

There are several precedents for this type of multiple stakeholder collaboration, and while we recognize the proposed REMS program will be a much larger effort than these have been, we do not think that its scope should prevent similar collaboration. These collaborative efforts include:

- Federal coordination on overdose prevention: ONDCP, SAMHSA, NIDA, DEA, CDC
 - Meetings between federal government agencies were held in 2008 to address concerns with prescription drugs. While the content of the meetings was not public, there exists a structure within which to discuss the coordination of opioid REMS and the complementary roles that each agency can take.
- Emerging Opioid Overdose Surveillance Group
 - Organized by CSAT/SAMHSA, this semi-monthly teleconference is well attended by representatives from government (federal, state, municipal), academic researchers, treatment providers, and community-based organizations. Opioid REMS have been discussed during these calls.
- Wilkes County (North Carolina) Chronic Pain Initiative and Project Lazarus
 - The Northwest Community Care Network (the regional Medicaid authority) and the Wilkes County Health Department have instituted a comprehensive community- and clinic-based system to address exceptionally high overdose death rates. The initiatives have had broad support from law enforcement, public health, clinicians, and the public. Many components of the community response resemble what has been proposed for opioid REMS.
- Pain Care Forum
 - A collaborative group of dozens of major stakeholders, the Pain Care Forum includes all the major pain organizations, patient groups and relevant professional groups, as well as opioid manufacturers and other healthcare industry and academic researchers.

2.2 Pilot to be used as Initial Phase for Proposed Long-Acting and Extended-Release Opioid REMS

We agree with recommendations made at the May 27-28, 2009 public meeting that a pilot to be used as the initial phase of the REMS would be an appropriate step. We additionally concur that methadone is the correct product for such an initial phase. We do believe, however, that geographic pilots with an emphasis on supply side reduction will not be effective, as demonstrated by the Wilkes County Chronic Pain Initiative in North Carolina, and will result in shifting the source of drug to neighboring regions without affecting the intended outcomes. A long-acting and extended-release opioid REMS based on supply reduction implemented regionally is likely to show minimal effectiveness, and cause confusion within the medical system. Combined with minimal effectiveness, regional differences in prescribing patterns, clinical practice, insurance coverage, and access disparities are likely to confound pilot evaluation and result in the conclusion that the pilot experiences are not generalizable.

We believe a nation-wide methadone REMS pilot would be a good model for the initial phase because:

- Methadone is one of the most researched opioid drugs included in the proposed class-wide REMS. Methadone has been used for decades and extensively studied in academia and by federal agencies.
- Learning from a methadone pilot would contribute to the development of the most appropriate REMS since methadone is a unique drug that requires specific prescribing practices and is used for two relevant indications (pain treatment and addiction treatment).
- Many federal agencies are already involved in the regulation of methadone (FDA, SAMHSA and DEA). Close cooperation between these agencies and other critical stakeholders (e.g., prescribers, treatment programs, etc.) could be effective.
- There has been a recent increase in methadone-related overdose deaths.
- Due to its generic status, methadone for analgesia has had little sponsored education (in contrast to branded opioids). But, there also has been little direct promotion, suggesting the increase in methadone prescribing has been affected by outside influences (e.g., health insurance rules, professional societies) which fall outside traditional means of FDA regulation. A methadone pilot as the initial phase presents a unique opportunity to test REMS components separate from other regulatory mechanisms to reduce unintended consequences.

It is also important to realize that while we are proponents of using methadone as the pilot medication, methadone does have unique characteristics that distinguish it from the other extended-release opioid products.

- It is prescribed for the treatment of pain and addiction in two different settings: opioid treatment programs and healthcare professionals' offices.

- It has highly variable inter-individual pharmacokinetics, requiring the prescriber to have an understanding of methadone's pharmacological properties to prescribe it appropriately.
- The dosing schedules for methadone depend on the indication for which it is being prescribed.
- Methadone is not considered a first-line pain medication; the other extended-release opioids are.

Although these differences may result in additional REMS elements for methadone, the intent of a methadone-specific REMS is to have as much similar content and elements as possible to the class-wide REMS.

We believe some aspects of the methadone REMS initial phase could be expanded to the extended-release opioids REMS on a rolling basis.

- A thoroughly tested and customizable Medication Guide could be implemented for one or more of the products without much delay.
- Critical baseline data for the extended-release opioids could be collected during this initial phase with methadone in order to put the appropriate pieces into place prior to implementation as required by FDAAA.
- All of the elements that would be critical for the success of the class-wide REMS could be phased in and tested prior to wider implementation.

2.2.1 Timing, Data Collection and Reports

We believe seven to twelve months must be allowed to collect baseline data and put the methadone pilot REMS in place. We recommend that the pilot be monitored for at least three years before appropriately tested and successful elements are applied to REMS for the other products, including the long-acting and extended-release opioid REMS.

The pilot REMS should include annual reports that are reviewed and discussed in concert with all stakeholders. The first report should focus on issues associated with implementation, lessons learned, baseline data, and potential modifications of the REMS to improve implementation, including experiences of pain patients. This would help to fulfill the FDAAA requirement that elements to assure safe use be assessed at least annually to determine the impact on safe use, burden on patient access, and burden on the health care delivery system. Subsequent reports may also include details about implementation of the REMS. The third annual report should include recommendations about whether and how to apply the REMS as a whole, or specific components of it, to long-acting and extended-release opioids.

3 Evaluation

FDAAA requires the evaluation of REMS. Evaluation is vital to guide implementation, quantify and characterize effects – both desired and unintended – and provide the basis for modification or even termination of elements of the REMS over time. The success

or failure of the proposed REMS will be determined by the evaluation results, and the evaluation will require the synthesis of studies from multiple sources. We have included below some recommendations with regard to the metrics that should be used to evaluate the proposed REMS, and the way in which those metrics should be used to evaluate it.

3.1 REMS Metrics

It will be critical to have baseline information for all metrics in place in order to evaluate any changes over time resulting from implementation of the proposed REMS. Further, it must be recognized that not all metrics may improve at first and that sufficient time must be given to collect and evaluate data. Although FDAAA specifies minimum time points for evaluation (18 months, three years, and seven years), we believe more frequent evaluation (i.e., every six months) is warranted for the proposed REMS due to the very large number of patients who could potentially be affected and the need to act quickly if negative unintended consequences are documented.

The metrics utilized to evaluate existing non-opioid REMS can serve as starting points for the evaluation of the long-acting and extended-release opioid REMS. Because there are important differences between existing REMS and the long-acting and extended-release opioid REMS, as described in Section 1.3 (Challenges of the Long-Acting and Extended-Release Opioid REMS) of this document, existing metrics will need to be carefully adapted if they are to prove useful. It will be critical to measure the effects of opioid REMS not only on the patient population for whom the drugs are prescribed, but also on non-patients who comprise the bulk of the population that bears the burden of the adverse events which are driving the implementation of the proposed REMS.

While we believe it is preliminary at this point to consider including the immediate-release (IR) opioids in the class-wide REMS, there will be advantages to using data related to the IR products to evaluate the REMS.

Items to measure will include at least seven categories:

1. Patient education (e.g., how many patients received the educational materials, their degree of patient comprehension of those materials, and who provided the materials to the patients). A potential data source for this category includes patient survey data.
2. Prescriber data (e.g., appropriateness of patient selection, medication errors, and overall comfort level of the prescriber with prescribing these medications). Professional societies could be a main source of data for this category. Professional societies could also be a source of data for process measures on the total number and rates of prescribers attending trainings, meeting certification requirements, etc. Additionally, private data, such as third-party claims data could be utilized for this metric. Qualitative information from and surveys of clinicians will be valuable to place practice-based quantitative assessments in context.

3. Adverse event data (e.g., changes in misuse, abuse or diversion of the products included under the proposed REMs, changes in the use of non-extended-release opioids and heroin to compensate for the restrictions of the REMS, and adverse event such as toxicological injuries associated with expanded or longer prescribing of immediate-release opioids containing acetaminophen and NSAIDs, such as hepatotoxicity and GI bleeds). Sources for this data include federally sponsored studies and proprietary data sources in addition to FDA's AERS.
4. Changes to access of medications. There are valid concerns about the proposed REMS disproportionately limiting access to opioids among populations that already have difficulty obtaining them, such as poorer patients, racial and ethnic minorities, and rural and inner-city residents.⁵ Physicians may choose to prescribe IR opioids or other prescription medicines not included in the proposed REMS, so any "switching" trends could be identified. In addition to patients currently receiving opioids, it will be important to prospectively follow individuals with chronic (and degenerative) painful conditions who are not yet on opioids in order to determine what other medications they are receiving instead of long-acting opioids. Previous experience in New York State with benzodiazepine prescribing suggests that patients may be placed on less safe medications as a result of medications being placed under greater controls.⁶ *Availability* of opioids before and after REMS implementation could be assessed using federally sponsored studies, claims data and sales data. However, to evaluate *access* to medications, focused studies in specific areas conducive to research are required to elucidate how the proposed REMS affects access. These studies will need to be designed quickly if they are to have enough baseline data, and should include qualitative and quantitative components. If methadone is to be the pilot, and additional requirements are placed on methadone maintenance treatment programs, access to methadone among individuals with opioid dependence disorders will also need to be measured.
5. Impact of the long-acting and extended-release opioid REMS. The total numbers of certified prescribers and providers, changes in demographics or type of pain treated, increases or decreases in prescription prices, etc. This information could be measured utilizing prescriber data sources and public use data sets.
6. Quality of life to patients. Do patients feel any increased stigma, note any changes in medication availability or any impact to their overall health as a result of the implementation of the proposed REMS? To measure changes over time after REMS implementation, these measurements should be done using patient surveys and standardized scales for quality of life. Equally important are serial in-depth qualitative interviews with existing patients on opioids and among those

⁵ Green CR, et al. Differences in prescription opioid analgesic availability: comparing minority and white pharmacies across Michigan. *J Pain*. 2005 Oct;6(10):689-99.

⁶ Portenoy RK. Therapeutic use of opioids: prescribing and control issues. *NIDA Research Monograph* 1993;131:35-50.

with physical degenerative conditions who are not on chronic opioid therapy, but are likely to require them during the evaluation period for the proposed REMS.

7. Costs. The impact on the public health system as a whole needs to be monitored and evaluated, including direct or indirect financial costs to patients. A thorough cost analysis will assist in determining the effectiveness and benefits of the REMS elements and identifying emerging cost patterns (e.g., differences due to geography, medical conditions, etc.) which are likely to influence the effectiveness of the proposed REMS. To obtain insight into the effects of the class-wide REMS, health economists should evaluate various data sources including patient and prescriber surveys, federal surveys, insurance billing data, and information from manufacturers.

Appendix I contains a table with a list of questions and metrics which should be addressed in the comprehensive evaluation for the long-acting and extended-release opioid REMS. The breadth of the questions posed points to the range of societal concerns held by different stakeholders, including the pharmaceutical industry, patients, potential patients, clinical providers and pharmacists. We have proposed a few datasets and study types which could be used to answer these questions. Many existing studies and data collection systems could be employed to provide general answers to these questions, but large variations in data specificity and quality are likely, and most existing data sources do not provide public use data in a time frame that would be necessary to inform decision making for REMS. Novel data collection mechanisms are also needed to assess specific questions related to the REMS, particularly documenting experiences and attitudes of stakeholders. While the tendency is to rely on quantitative data sources, some of the most important information, especially initially, will come from qualitative sources. Formal qualitative studies are warranted, in addition to evaluation of the spontaneous comments generated on the Internet and by news media. The design of any pilot (e.g., methadone for analgesia and opioid addiction) will strongly influence the nature of evaluation, and efforts should be made to integrate evaluation with implementation.

As outlined in Appendix I, existing data collection systems funded and conducted by the federal government can be used to address specific questions associated with the proposed REMS related to general health status, health behaviors, and access to and use of prescription medications. However, there is considerable delay in making these data available to the public, more than four years in some cases such as National Health and Nutrition Examination Survey (NHANES) and National Ambulatory Medical Care Survey (NAMCS). We recommend that FDA take the lead in convening the researchers at federal agencies who are collecting these data to determine if more rapidly available data could be assembled for use in the evaluation of the proposed REMS. It is likely that additional staffing resources may be required to assist these allied agencies in assisting with specific evaluation or data requests. Without this level of coordination between federal researchers, and the potential for increased staff, valuable tax payer-funded tools may not be utilized in a timely fashion to evaluate this pressing public health concern. In their current form, these data could be used for retrospective evaluation at the seven-year required time point, but are unlikely to be of

much use in informing more immediate decisions regarding evaluation of pilot REMS components. However, without coordination at the federal level, it is unlikely that causal conclusions can be drawn from these studies, even at the later time point, due to the lack of information on whether individuals were “exposed” to components of the opioid REMS, discussed below. Data from these studies will be of use insofar as they are combined with other data sources, and used as one component of a multi-faceted evaluation plan.

3.2 Evaluation of REMS Data

The evaluation of the long-acting and extended-release opioid REMS will not be limited to the analyses agreed on between the agency and industry. The availability of electronic data from different sectors of healthcare (e.g., pharmacy claims, emergency department admissions, urine screening, etc.), increasing computing power and widespread academic interest ensure that analyses of varying quality will be conducted by various individuals/groups. These analyses will undoubtedly drive public and professional opinions on the effectiveness and unintended consequences of the proposed REMS.

The evaluation of opioid REMS will require simultaneous input from multiple data sources and population- and clinic-based studies. Reconciling findings across studies will pose a distinct challenge and will require due consideration of methodologies and potential biases of researchers. While development of new research strategies and interesting questions should not be dissuaded, it is very important to agree ahead of time (i.e., before implementation of any REMS) on a series of core metrics that will comprise the fundamental basis of evaluation, including specific hypotheses that will be tested. As in a clinical trial, concerns about multiple testing are relevant in the post-marketing setting as they pertain to evaluation of opioid REMS. Given the large number of data sources that could be used to inform the debate and wide interest among researchers, as well as the indirect method of intervention authorized by FDAAA, the possibility of conflicting results is predictable. Deciding on which metrics comprise the core should be done in a transparent manner with input from representatives of pain patients, industry, federal agencies collecting data, and academic researchers. Many existing large, federally-sponsored public health studies (e.g., NHANES, MEPS) have the potential for answering some of the questions posed, but may require the addition of questions or modification of existing questions.

One specific concern with evaluation metrics is determining whether a survey respondent or individual with an adverse event was “exposed” to the REMS. Many of the proposed studies are ecological in nature, due to the nature of the data sources and the expense associated with creating new ones for the specific purpose of evaluating REMS. The methodological pitfall of focusing on outcome-based metrics (e.g., emergency department admissions, changes in prescribing behavior) is that these outcomes could be heavily influenced by other policies and interventions being simultaneously implemented.

For example, formulary changes by insurance companies, initiatives to increase use of prescription monitoring programs, large scale law enforcement interdictions to reduce

diversion, changes in indication, media coverage about safety, and actions by state medical boards can all influence the amount of medication in use, as well as the unintended consequences attributed to the REMS. Ideally, prospective cohorts of patients covered by the REMS would be needed to provide meaningful results, even at the expense of national coverage or generalizability. At a minimum, a policy bank should be developed and updated to document national, regional, state and commercial practices and policies which impact opioid prescribing. Similar databases have been created for monitoring economic policies, especially in situations where researchers looking at national data may not be aware of less publicized policy changes. It is critical to account for sub-national actions and events which affect opioid prescribing, and that such a database is made available to all researchers attempting to evaluate REMS. The availability and acceptance of multi-level modeling techniques in epidemiology has advanced to the stage expectation that geographic variations in policy are accounted for. The credibility of the evaluation of opioid REMS hinges upon our ability to account for potential confounders in necessarily ecological analyses.

4 Educational Materials

Instructional or educational materials that will be used by patients, prescribers, and/or pharmacists are a critical component of any REMS. These materials could include medication-specific information for patients, such as Medication Guides, or opioid-specific information relevant to prescribing and dispensing practices for physicians and pharmacists. Below, we offer some recommendations as to the development and evaluation of educational materials that might be included in the proposed REMS.

4.1 Assessment of Educational Materials

Educational materials used as part of the proposed REMs should be evaluated both pre- and post-marketing. Any pre- and post-market research on REMS educational materials should be submitted to FDA as demonstration of the validity and effectiveness of the materials. Therefore, throughout each stage of any research program on educational materials, sponsors should document adherence to standards of behavioral research through protocols, interview guides, data analysis plans, and final study reports.

4.1.1 Qualitative Pre-Distribution Assessments

The development of any educational materials should include testing for clarity and comprehension in the target populations prior to their actual distribution and use in-market. Qualitative research should be done with the relevant target populations to assess the extent to which the materials convey the most important information for safe and effective use of long-acting and extended-release opioids. This research should assess respondent's knowledge of key information (to be determined *a priori*) following exposure to the educational materials. Label comprehension testing undertaken for OTC Drug Facts Labels serves as a valuable precedent for similar research. Similar research strategies and methods could be applied to REMS educational materials. The results of the pre-market, qualitative research should be used to modify the educational materials before distribution and use in-market if they are found to be unclear or deficient.

4.1.2 Quantitative Post-Distribution Assessments

Following distribution and use of REMS educational materials in-market, post-marketing evaluation would allow for assessment of the real-world reach, effectiveness, and impact of the educational materials. Quantitative research with the relevant populations should be conducted. For example, to assess whether patients are receiving, understanding, and complying with educational materials for a particular long-acting and extended-release opioid drug, surveys could be conducted among samples of patients who have been prescribed the drug. Similarly, surveys could be developed for prescribers and/or pharmacists to assess knowledge of the information contained in the educational materials for particular drugs.

5 Conclusion

Pinney Associates hopes that this perspective on the desired outcomes and potential challenges involved in the development and implementation of the class-wide long-acting and extended-release opioid REMS presents a clear picture of some of what lies ahead in attempting to develop and implement this program. The thoughts we have presented here related to key potential public health issues, the development and implementation process, the evaluation process, and the development of educational materials only touch on some aspects of what will be an enormous effort. It will be necessary to have realistic expectations of the outcomes and to use an iterative process to make adjustments to the program as needed. We will all learn a tremendous amount as the process moves forward and will need to be adapt as needed. Flexibility by all stakeholders will be key to avoiding harmful consequences.

The following is a summary of our key messages:

- Public Health Challenge
 - Given the long history of the abuse of opioids, including prescription opioids, in the U.S., the development and implementation of a class-wide long-acting and extended-release opioid REMS is timely.
 - While developing and implementing a REMS program that can cover all aspects of abuse, addiction, misuse and overdose of these products will be challenging, it is imperative that thought be given to key public health considerations with the appropriate focus on the potential impact on both the intended population for these medications, pain patients, and the populations of unintended users. For example, success will only be achieved if attention is paid to both supply and demand side aspects of the problem. If a compassionate use program is considered as part of a proposed REMS, research should be done to assess what the potential impact, including the potential unintended impact, might be before it is implemented.
- Process
 - All stakeholders should be identified and included in the REMS process, and decision-makers held accountable for working collaboratively with

these stakeholders to develop, implement, evaluate and, if needed, improve the class-wide REMS for the long-acting and extended-release opioid.

- Utilizing a methadone REMS as a pilot will enable study of elements to be included in the proposed REMS and the impact of a REMS on a smaller but relevant population. This pilot will provide the opportunity not only to test important elements of the proposed REMS, but to begin the process of bringing in all the relevant stakeholders including relevant governmental agencies (i.e., FDA, NIDA, DEA, ONDCP, SAMHSA).
- Evaluation
 - It will be critical to choose the correct metrics to measure the effects of the long-acting and extended-release opioid REMS not only on the patient population for whom the drugs are prescribed, but also on non-patients who account for the majority of the cases that showed up in the data that resulted in the request for the REMS.
- Educational Materials
 - The educational tools used in the proposed REMS must be tested in advance following standards of behavioral research and implemented in a careful fashion to ensure the right messages are being conveyed to the right audience.

We look forward to any further opportunity to work with FDA and other stakeholders on developing and implementing a class-wide long-acting and extended-release opioid REMS that effectively minimizes non-medical use of these products, without reducing access among those pain patients who need them.

Respectfully submitted,

Sidney H. Schnoll, M.D., Ph.D.
Vice President, Risk
Management Services, Pinney
Associates
and
Virginia Commonwealth
University
and
University of Kentucky

Jack E. Henningfield, Ph.D.
Vice President, Research and
Health Policy, Pinney
Associates
and
The Johns Hopkins University
School Of Medicine

Emmanuelle St. Jean, MPH
Associate, Pinney
Associates

Nabarun Dasgupta, MPH
University of North Carolina
Gillings School of Global Public
Health, Chapel Hill
and
Scientist, Pinney Associates

Michelle D. Ertischek, MPH
Senior Associate, Pinney
Associates

APPENDIX I

Metrics to be Measured in Class-wide REMS

Prepared by Pinney Associates

Metric	Potential Data Source(s)
<p>Patient Education</p> <ol style="list-style-type: none"> 1. Did patients receive Medication Guide (MedGuide)? 2. Did they understand the MedGuide? 3. Do patients understand Patient-Prescriber Agreement (PPA)? 4. From whom did the patients receive PPA? 5. Did anyone review PPA with the patient? 6. Have patients translated the information into appropriate use and best practices? 7. Why were you prescribed the long-acting or extended-release opioid? 	<p>Patient Surveys</p> <p>Public Data:</p> <ul style="list-style-type: none"> ▪ National Health and Nutrition Examination Survey (NHANES)
<p>Prescriber</p> <ol style="list-style-type: none"> 1. Are the appropriate patients being selected to receive the medication? 2. Are medication errors occurring (e.g. inappropriate dose level)? 3. Has the comfort level among prescribers changed since REMS implementation? 4. Are prescribers being reimbursed for patient education 	<p>Prescriber Surveys</p> <p>Private Data:</p> <ul style="list-style-type: none"> ▪ Third-Party Payer Claims Databases

Metric	Potential Data Source(s)
<p>Adverse Events (AEs)</p> <ol style="list-style-type: none"> 1. Has there been a change in misuse, abuse, diversion, and overdose deaths resulting from use of long-acting or extended-release opioids? 2. Has there been an increase or decrease in street access to medications? 3. Has there been an increase or decrease in extended-release versus immediate-release prescription opioids? 4. Has there been an increase in the availability of counterfeit products? 	<p>Public Data:</p> <ul style="list-style-type: none"> ▪ DAWN ▪ FDA MedWatch ▪ National Survey on Drug Use and Health (NSDUH) ▪ Medical Expenditure Panel Survey (MEPS) ▪ National Hospital Discharge Survey (NHDS) ▪ National Poison Data System ▪ National Vital Statistics Report <p>Private Data:</p> <ul style="list-style-type: none"> ▪ NAVIPPRO ▪ Pharmaceutical Proprietary Data ▪ RADARS System ▪ Third-Party Payer Claims Databases
<p>Access</p> <ol style="list-style-type: none"> 1. Do various populations (e.g. rural, elderly, and other vulnerable populations) continue to have access to long-acting and extended-release medications? 2. Have disparities in access emerged? 3. Has there been a change in coverage for extended-release opioids? <ol style="list-style-type: none"> a. Are extended-release opioids on an insurance company's formulary? b. Has there been an increase in purchasing pools? <ol style="list-style-type: none"> i. Are public and private organizations forming pools to purchase these products? 4. Are patients experiencing difficulty in paying for their prescriptions? 5. Are more patients obtaining products from foreign countries? 6. Is there an increase in the number of patients admitted to opioid treatment programs that are there primarily for pain treatment? 	<p>Public Data:</p> <ul style="list-style-type: none"> ▪ Medical Expenditure Panel Survey (MEPS) ▪ National Ambulatory Medical Care Survey (NAMCS) ▪ Patient Surveys <p>Private Data:</p> <ul style="list-style-type: none"> ▪ IMS ▪ RADARS OTP survey ▪ Third-Party Payer Claims Databases

Metric	Potential Data Source(s)
<p>Impact of REMS</p> <ol style="list-style-type: none"> 1. What is the number of certified prescribers? 2. What is the number of participating pharmacies and pharmacists? 3. How many patients are prescribed extended-release opioids? 4. Has there been a change in the type of medications prescribed? <ol style="list-style-type: none"> a. Are long-acting prescription opioids being prescribed more or less than short-acting opioids? 5. Which patients are receiving extended-release opioids? <ol style="list-style-type: none"> a. Has there been a shift in demographics? b. Are patients with particular ailments (e.g. back pain, fibromyalgia, etc.) receiving extended-release opioids? 6. Has there been an increase or decrease in government regulation of drug prices? 7. Has there been an increase in awareness among the public regarding extended-release opioids? 	<p>Public Data:</p> <ul style="list-style-type: none"> ▪ Medical Expenditure Panel Survey (MEPS) ▪ Legislation ▪ National Ambulatory Medical Care Survey (NAMCS) <p>Private Data:</p> <ul style="list-style-type: none"> ▪ IMS ▪ Third-Party Payer Claims Databases
<p>Quality of life</p> <ol style="list-style-type: none"> 1. Do you feel stigmatized by the prescription? 2. Has your prescriber been suspicious of your use of the medication? 3. Have you had difficulties in obtaining your prescription at the pharmacy? 4. Has the patient's health outcome improved? 	<p>Patient Surveys</p> <p>Prescriber Surveys</p>

Metric	Potential Data Source(s)
<p>Costs</p> <ol style="list-style-type: none"> 1. Has the cost of the medication increased since implementation of the REMS? 2. Are prescribers being reimbursed for education? 3. What is the cost of the REMS program? <ol style="list-style-type: none"> a. What are the administrative costs? b. What is the cost of the REMS program to the health care system? 4. Has a company's product pipeline been affected? 	<p>Cost Analyses performed by Health Economists</p>

Potential Data Sources for the Proposed Class-wide REMS

Prepared by Pinney Associates

Acute poisoning events: AAPCC NCS Beta/National Poison Data System

The National Poison Data System is maintained by the American Association of Poison Control Centers (AAPCC). The data is comprised of human exposure cases and information calls to all US poison centers. The Information collected is based on spontaneous, self-reported calls, which is a limitation in the use of this system. Data are only available after one year, and have been shown to contain considerable discrepancies regarding the coding of drugs involved, and this dataset does not contain the call notes, which are used for quality assurance purposes and to provide context for events reported.

Drug Abuse Warning Network (DAWN)

DAWN is a surveillance system managed by the Substance Abuse and Mental Health Services Administration (SAMHSA). DAWN monitors drug-related visits to hospital emergency departments (DAWN-ED) and drug-related deaths investigated by medical examiners and coroners (DAWN-ME). DAWN-ED obtains its data from a sample of hospitals operating 24-hour emergency departments tracks ED visits related to or resulting from substance abuse. DAWN-ME collects data from a sample of medical examiners. DAWN-ED data are routinely used to track the impact of treatment seeking for acute events arising from the misuse and abuse of extended-release opioids. However, DAWN ED mentions are not limited to acute presentations related to abuse, misuse and addiction; treatment seeking for detoxification is a major component of the admissions recorded in this system, artifacts of the paucity of demand reduction measures available to individuals and requirements of insurance reimbursement. DAWN ED data must be interpreted with caution.

DAWN has some limitations. First, DAWN data cannot be interpreted as prevalence measures since DAWN ED monitors episodes and not individuals. The DAWN hospital sample has lost multiple major US cities in the past year. In addition, no distinctions are made between prescription drugs being taken as prescribed and the medication(s) being abused that resulted in the ED visit. Finally, data is not submitted in “real time” because the data must be collected, analyzed, and reported. In the case of DAWN ME, data are delayed by four years, significantly limiting the use of this component of DAWN.

FDA MedWatch

FDA MedWatch is a voluntary spontaneous reporting system that collects information about adverse events or reactions to medications, drug products, and medical devices. Additionally, it provides new safety information on medications. MedWatch can be monitored for emerging trends in adverse events.

National Ambulatory Medical Care Survey (NAMCS)

The National Ambulatory Medical Care Survey (NAMCS) is a national survey, conducted by the Centers for Disease Control and Prevention, and administered to primarily to non-federally employed office-based physicians primarily engaged in direct patient care. As of 2006, physicians in federally qualified community health centers were also surveyed. This survey is not completed by anesthesiologists, pathologists, and radiologists.

The purpose of the survey is to obtain information about the provision and use of ambulatory medical care services in the U.S. Physicians are randomly assigned a 1-week reporting period and physicians or office staff record information on a systematic random sample of visits. Data on patients' symptoms, diagnoses, and medication prescribed or provided to patients are collected. NAMCS has been collecting medication data since 1980. Additionally, patient demographics (e.g., age, sex, race, household income, and education), diagnostic procedures, patient management, and planned future treatment information, and source of payment are collected.

The data collected on medications used for pain treatment may be useful because they can be used along with physician characteristics (e.g., specialty) to analyze physicians' prescribing behaviors. However, a limit that exists with the NAMCS survey is that providers can list up to eight drugs on the survey medicine. In addition, the survey is dependent upon what is documented in the medical record. Incidence, prevalence, and state-level estimates cannot be determined using NAMCS data. There has been a decrease in the number of physicians participating in the survey in recent years. This can potentially affect generalizability. Data for public release are delayed by four years, limiting the use of this datasource without cooperation from CDC.

National Disease and Therapeutic Index

The National Disease and Therapeutic Index (NDTI) monitors the treatment patterns of 350,000 private-practice physicians, and is a commercial product offered by IMS Health. Physicians report on a quarterly basis on all the patient contacts that have occurred during a single two day period. Patient demographics, diagnosis, and treatment (including medication prescribed) are collected and can be used to identify the patient populations receiving extended-release opioids and measure prescribing trends. Due to the time-limited sampling of NDTI, linking diagnoses for chronic conditions to medications prescribed may not be feasible.

National Health and Nutrition Examination Survey (NHANES)

The National Health and Nutrition Examination Survey (NHANES) is administered by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC). NHANES assesses the health and nutritional status of children and adults in the US. Participants are interviewed and undergo a physical examination. Although there are limited questions about pain and medication used, this survey can be used to determine if behavioral changes have occurred in the long term.

National Hospital Ambulatory Medical Care Services

The National Hospital Ambulatory Medical Care Services collects data annually from non-institutional general and short-stay hospital outpatient and emergency departments during a 4-week period. Federal, military, and Veteran Administration facilities are not surveyed. Information regarding the provider (e.g. hospital ownership, geographic information, practice information), patient demographics, visit characteristics (source of payment, continuity of care, reason for visit, diagnosis, treatment plan) is collected in addition to medication information. NHAMCS also collects data regarding the opioids prescribed by pain severity.

Like the National Ambulatory Medical Care Survey, the data collected can be used to determine changes in prescribing practices and identify trends. Incomplete responses and biases due to survey and item non-response may affect the results obtained.

National Hospital Discharge Survey (NHDS)

The National Hospital Discharge Survey (NHDS), conducted by the Centers for Disease Control and Prevention, is an annual chart abstraction of inpatient discharge records from a national sample of 500 non-federal, non-institutional, short-stay hospitals in the U.S. Records are coded using ICD-9-CM, which has known limitations regarding admissions and discharges associated with chronic painful conditions, substance abuse and overdose. Hospitals with fewer than six beds staffed for patient use are excluded from this survey. Since, the NHDS captures information on the medication prescribed to patients, trends regarding medications prescribed and used in a hospital setting. These data are delayed by five years, and have therefore have limited utility in this setting.

National Survey on Drug Use and Health (NSDUH)

National Survey on Drug Use and Health (NSDUH) is a household-based survey administered yearly by the Substance Abuse and Mental Health Services Administration (SAMHSA). It is the leading source of statistical information on the use of illicit drugs and the nonmedical use of prescription drugs among civilian, non-institutionalized U.S. population, 12 years of age and older. The survey obtains information on the illicit use of marijuana, cocaine, heroin, hallucinogens, inhalants and the non-medical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives. Survey respondents are asked if they have abused methadone, morphine, and OxyContin.

The national- and state-level data on the prevalence, patterns, and consequences of prescription drug use would provide information as to whether there has been a change in the non-medical use of prescription pain relievers since the classwide REMS was implemented. However, it is important to note there are limitations to NSDUH data. NSDUH only obtains information on the “lifetime” non-medical use of specific prescription brands. In addition, the survey questions do not differentiate between abuse by a person to whom the medication was prescribed and abuse by a person for whom the medication was not prescribed.

National Vital Statistics Data

National Vital Statistics Data are maintained by the National Center for Health Statistics of the Centers for Disease Control and Prevention. Data from the national vital statistics can be used to identify the number of overdose deaths in the United States due to prescription opioids. For example, cause of death data can be used in conjunction with prescribing trends obtained from other data sources to determine if there is a relationship between the variables. Publicly available data are delayed by four years, limiting the usefulness of national vital statistics data for informing REMS evaluations, although state vital statistics data may be available earlier for evaluations in specific areas. Vital statistics data in the United States are coded using ICD-10, which has very limited product specificity; methadone is the only pharmaceutical opioid which has its own code. Heroin also has its own code and these data can be used to identify any shifts in heroin-related mortality after REMS evaluation. Case attribution concerns are common with mortality data, as there is no national standard for when to perform an autopsy, how to conduct toxicology panels, and how to interpret the results.

NAVIPPRO™

Inflexxion, Inc.’s NAVIPPRO™ surveillance system collects data from enrollees in substance abuse treatment facilities located in a number of states. Data are collected using a computer interface, and based on the Addiction Severity Index (ASI). Enrollees complete the assessment in the course of care. Enrollees are a heterogeneous mixture of voluntary treatment seekers and those mandated by the criminal justice system, and the services offered by the treatment facilities are varied in terms of clinical and psychosocial care, making data interpretation difficult. Data are collected in real time and can be analyzed rapidly, and contain detailed information on routes of administration. These data could be used as an adjunct for other data sources monitoring the treatment seeking (usually non-patient) population for changes in drug preferences and routes of administration.

Medical Expenditure Panel Survey (MEPS)

The Medical Expenditure Panel Survey (MEPS) is conducted annually by the Agency for Healthcare Research and Quality of the Department of Health and Human Services. The Household Component (MEPS-HC) conducts interviews with a nationally representative sample of the civilian non-institutionalized adult US population. Families, individuals, and their health care providers (pharmacies, physicians, hospitals, etc.) are surveyed to obtain information on specific health services received, frequency of

utilization, and financial cost of these services. In addition, information regarding the type of medications prescribed, dosage, and payment method is collected; respondents are asked about their use of prescription medications and permission to verify the responses with their pharmacy. MEPS can be used to determine trends in the use of extended-release opioids, number of prescriptions purchased, and total financial costs. MEPS-HC has been used to document differences in prescription analgesic use and access by race (Stagnetti⁷). Exacerbating existing disparities in access to opioid medications is a principal concern of patient advocacy groups. Because MEPS does not collect data on prescription drugs obtained during hospital visits, trends will only be identified for the outpatient population. These data are delayed for public release by about one year.

Patient Surveys

Patient surveys will be administered to patients prescribed extended-release opioids and potential patients of extended-release opioids. The patient survey is an essential tool to be used in evaluating whether the classwide REMS is increasing patient awareness regarding extended-release opioids and addiction. The survey will be assessing periodically patients' comprehension and understanding of appropriate pain medication use and storage. The survey will also determine if patients are receiving the Medication Guide and Patient-Prescriber Agreements.

Pharmaceutical Proprietary Data

Pharmaceutical companies collect information on the misuse, abuse, diversion, and overdose deaths resulting from the use of their products. In addition, proprietary data will also provide insight into whether there has been a shift from extended-release opioids to immediate-release opioids. These data will help in assessing misuse, abuse, and diversion trends.

Policy Bank

Policy changes at national, regional, state and local levels will directly affect local supply of extended-release opioids. For example, changes in state Medicaid prior authorization structures, major law enforcement operations, and initiatives to expand access to drug treatment services can change local dynamics and make overall assessment of the proposed REMS difficult. In order to lend validity to ecological analyses of the REMS, a centralized database of relevant policy changes and interventions will need to be documented and made accessible to researchers. Policy changes and interventions can be monitored electronically through targeted scraping

⁷ Stagnitti M N. Trends in Outpatient Prescription Analgesics Utilization and Expenditures for the U.S. Civilian Noninstitutionalized Population, 1996 and 2006. Statistical Brief #235. February 2009. Agency for Healthcare Research and Quality. Rockville, MD.
http://www.meps.ahrq.gov/mepsweb/data_files/publications/st235/stat235.pdf

and storing of information from websites, as well as through user generated content collected prospectively.

Prescriber Surveys

The prescriber surveys will be administered to a representative sample of prescribers in the US. This survey will capture information regarding the patients selected to receive extended-release opioids, comfort level of prescribers since the implementation of REMS, and whether prescribers are being reimbursed for patient education. The results of this survey can be used to assess the impact of the class-wide REMS on key stakeholders and prescribers.

Prescription Drug Data from Hospital Associations

Data obtained from hospital associations may assist in identifying utilization and prescribing trends in hospitals. Although this information is also collected by the National Hospital Ambulatory Medical Care Services (NHAMCS), more hospitals participate in hospital association surveys than in NHAMCS.

RADARS[®] System

The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS[®]) System is based in the Rocky Mountain Poison and Drug Center and the Denver Health hospitals. It collects brand- and geographic-specific data on misuse, abuse, and diversion using six Signal Detection Systems (SDS): Drug Diversion, Poison Centers, Survey of Key Informant Patients, College Survey, Healthcare Workers, and Opioid Treatment Programs. The SDS are designed to collect information on the continuum of drug use disorders, from acute events reported to poison centers to dependent treatment seekers entering drug treatment facilities. The data are aggregated to the three-digit ZIP code level, and used to calculate rates which can then be analyzed to identify geographic and time trends within the context of product availability in a particular community. Historical data go back to 2002, providing baseline information for assessment. Data are reported quarterly, with a one quarter reporting time lag, and are product specific.

Limitations are that a handful of poison centers do not participate in the system, there is limited use of standardized scales for assessing drug abuse/dependence, and most SDS rely on self-reported information.

Sales Data: Commercial Data Vendors

Multiple commercial data vendors collect information on the number of prescriptions dispensed in outpatient settings in the United States using probability samples drawn from reimbursement software installed in pharmacies, including IMS Health and SDI. Product-specific data are available with a lag time of only a few months, and these data sources are routinely used by industry and FDA. Data obtained from these sources can be applied to identify prescribing patterns and shifts, for example from extended-release to immediate-release opioids. In the context of a methadone pilot, such data would be

very important to know if there was a general shift away from methadone prescribing in favor of extended-release opioids. The main limitation is that the number of prescriptions are based on a probability sample (i.e., less than full coverage of all outpatient transactions in the US), giving rise to less precise estimates in rural areas. Sales data such as these are difficult to analyze by the number of kilograms sold given issues of potency between painrelievers, and the number of prescriptions, because of different regulations and beliefs associated with different scheduled classes.

Third-Party Payer Claims Databases

Third-party payer claims databases collect prescription information, insurance billing data, and existence of purchasing pools. The products vary considerably on their data quality, especially with regard to chronic illness diagnoses. All products have substantial limitations of generalizability. The information acquired from these databases will provide insight into whether prescribers are being reimbursed for patient education, assess prescribing patterns, determine financial costs to the patient and healthcare providers. Researchers have used data from third-party payer claims database to evaluate the association between care and formulation changes of prescription drugs, examine the dosage and titration patterns of extended-release medications, the direct and indirect financial costs o for particular illnesses. These data can be used, with significant limitations, to link diagnoses codes to particular medications. Reviewing health insurance claims data will provide insight into whether prescribers are being reimbursed for patient education, prescription coverage, existence of purchasing pools, and prescribing trends. Furthermore, claims data will assist in determining the total and incremental cost of the proposed classwide REMS.