

Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor, Boston, MA 02109

September 28, 2016

Re: Institute for Clinical and Economic Review (ICER) Draft Scoping Document on Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Areas of Agreement

As the Document allows ICER to take into account both positive and negative outcomes associated with payer, provider and legislative policies surrounding ADFs, it has the potential to adequately capture the dynamics of the ADF development and deployment. Overall, the background in the document is positive and includes several important points that are fair, balanced and should remain in the final conclusions adopted by ICER:

- ADFs are an inclusive part of the concept of *"integrative pain management."*
- Successful formulation of Schedule II products with ADF characteristics still includes the possibility of misuse, abuse, diversion, and subsequent addiction.
- The specified outcomes in the document are supported by the ADC as they are relevant to "real-world" manipulation, abuse and diversion scenarios. In particular, the following outcome measures have the most relevance for measured benefit of ADFs:
 - o Real-world outcomes
 - Lower rate of diversion
 - Lower street value
 - Switch to other opioids for non-therapeutic use. NOTE: May include switch to heroin
 - Clinical outcomes
 - Non-therapeutic opioid use
 - Dependence and/or addiction (new cases and relapse)
 - Emergency department and hospital utilization
 - Overdose
 - Death

The ADC believes that either one or both randomized controlled studies (RCT) of drug liking as well as real-world observational studies utilizing appropriately selected comparators (such as data made available by RADARS or Inflexxion), in addition to measures of pharmacokinetics and in vitro testing, are appropriate measures of incremental deterrence capabilities as the ADF market continues to develop.

- Current coverage policies by payors may be limiting access to appropriate treatment of patients with pain, especially in rural areas. This lack of coverage will impede utilization and limit outcomes data necessary to determine future ADF coverage decisions a self-fulfilling negative feedback loop.
- Non-opioid pain strategies and addiction treatment will not be considered as comparators for the purpose of determining ADF effectiveness. However, the ADC understands those issues will be discussed at the March 23, 2017 public meeting.

Areas of Potential Concern

There are also areas of potential concern, depending on significance and interpretation, in the document.

- ICER specifically points out the lack of ADFs addressing intact oral abuse, which could be used to discount the benefits of existing technology recognized by FDA labeling. This could be:
 - Positive if meant as a needed incentive to the nascent industry of ADF innovators to continue aspirational efforts to developing technologies that address oral abuse.
 - It is important to note that select opioids have ADFs that address oral abuse via administration of chewed/crushed ER formulations. Oral administration of manipulated ER formulation poses increased safety risk in comparison to administration of intact formulations.
 - ICER's position on oral abuse would be appropriate in a mature market abuse deterrence is a new technology and, as such, the emphasis is more appropriately focused on incremental improvements in nascent technology.
 - Negative if it is criticizing ADFs current success for having not yet achieved something for which ADFs are not currently designed.

- Intact oral abuse is not currently a route that can be deterred by approved ADF technologies. A solution to "super-therapeutic dosing" (taking more pills than prescribed) requires more research.
- Current ADF technologies disrupt the "abuse progression" cascade, which in effect results in stopping the progression from taking too many intact oral doses of a psychotropic drug to dosage manipulation prior to oral abuse through abuse via alternate routes of administration (intravenous, intranasal, inhalation).
- ICER should use like products for active comparators. Extended-release (ER) opioid ADFs should be compared with a non-ADF version or an ADF version of a similar (same active moiety) product.
 - ER opioids have a relatively large dose of active pharmaceutical ingredient (API) designed to release slowly over time, typically treating the patient for 10-12 hours.
 - IR opioids have a relatively small amount of opioid that is immediately released and patient treatment lasts four to six hours.

For clarity, all ADFs should be judged on both therapeutic effectiveness (which would be expected to be similar for each API and likely for the opioid class), as well as on abuse-deterrence capabilities compared to non-ADF versions of similar products.

- The report also leaves open the possibility that ICER could specify price thresholds based on its assessment of value, and create a budget impact model based on erroneous and imprecise uptake assumptions.
 - ADF technology is at its most early stage, with seven extended release/long-acting opioids receiving FDA labeled indications for abuse deterrence. The FDA has only approved an ADF label for seven ER opioid products and no IR opioid products. The earliest approval is only three years old and most approvals have occurred in the recent months.
 - The ICER assessment risks being too early in the lifecycle of ADF technology to provide useful information for payer, physician and/or patient consideration.
 - The analytical framework in the scoping document states that in the analysis, ICER will employee a pre and post time series analysis approach. Except for one ADF opioid, because of the early stage of ADF technology development, none of the other approved opioids with an ADF label have pre- and postreformulation to ADF post marketing data available, which will limit the utility of this proposed analytical approach.

An unintended consequence of this early action could be to potentially lead stakeholders to erroneous, or incorrect, conclusions about the value of ADFs. In turn, this could set the ADF development effort back, resulting in unintended growth in the Rx drug abuse epidemic by delaying or limiting access to ADFs. Another unintended consequence could be that patients in need of pain management will lose access to effective pain therapies.

- The document proposes that potential benefits and market penetration will be assessed in the context of "*coverage policies and legislation*." This could be positive if it assesses the negative impact of policies reducing access, but could be negative if ADF legislation is incorrectly presumed to significantly grow the overall opioid market.
- The Document appears to imply that ADFs may not be recommended for cancer/palliative care patients, since ICER is likely to find that most published studies exclude this sub-group.
 - Regardless of the etiology, and hence the patient population, ADFs manage severe pain and should be available to all appropriate patients as determined by the prescriber. ADF characteristics that mitigate abuse, misuse, diversion, and addiction transcend patient populations and are equally relevant to all patients, their caregivers, and their families and friends who are potentially subject to this epidemic. Therefore, restricting access to cancer/palliative care patients because they were not studied in clinical studies, and, thus, not in the published literature, does not make intuitive sense, and could lead to significant harm in these patients.
 - The ADC membership supports ADF for all C-II products, regardless of the population served by the treatment. This is a critical consistency as cancer/palliative care patients are not excluded from the risk pool for misuse, abuse and diversion of their pain therapies especially diversion, as the constant pool of visitors, caregivers and support individuals are a demonstrated risk point.
- Finally, in the four identified populations expected to be studied (listed below), the ADC recommends that the last category specify persons addicted to "prescription" opioids. Failure to do so leaves open the inappropriate inclusion of heroin or other non-prescription opioids.
 - Patients with non-cancer chronic pain, stratified by age group where feasible
 - Patients with cancer, with particular attention to cancer patients in palliative care
 - Recreational drug users
 - Patients with opioid use disorder

Cost / Benefit Analysis

It appears clear that the model ICER will construct from this evaluation will be from the payor perspective of direct health care costs. And if data are available, a model may be constructed from the societal perspective, recognizing the effects of ADFs

outside of the healthcare system. The ADC is committed to assisting ICER in the acquisition and evaluation of studies necessary to arrive at a fair and balanced outcome that reflects both the current state of ADF development and deployment, as well as outcomes based on "real-world" scenarios. In particular, studies should cover cost effectiveness in a dynamic, rather than static fashion. Both the cost to implement ADF, as well as the offsets caused by reduced manipulation, abuse, and diversion should be covered. As ICER typically would seek to develop data that would fit within the Quality-adjusted Life Years (QALY) model, the concern is that insufficient data are currently available for an equitable analysis.

At this point in the life-cycle development of ADF technologies, cost per QALY analysis, threshold analysis, and/or costconsequence analysis are all likely to fail due to insufficient information to determine a reasonable effect. For example, the one product that can be reviewed that has a "before ADF" price point and an "after the reformulation to ADF" price point is Purdue Pharma's OxyContin.; there is no price difference between the two versions of the product. Similarly, Endo currently markets a version of Opana ER with what the company believes are ADF technologies while seeking an approved ADF label and had earlier marketed a version with no ADF technology/features. Both products carry identical pricing.

The ADC is concerned that a 5-year horizon budget impact model based on 5-year estimated uptake would greatly overestimate the impact to payors, possibly suggesting the need for managing the cost of ADFs. At this stage in the development of all forms of abuse deterrent technologies, the risk of such an evaluation could be to halt the development of these technologies that are an important part of the prevention formula to ultimately significantly reduce prescription drug abuse.

Final Thoughts

Thank you for the opportunity to express the views of the ADC and all of the undersigned Members are available to work with ICER in the further development of this proposed Report.

Dan Cohen Abuse Deterrent Coalition Chairman

Marsha Stanton, PhD, RN Pernix Therapeutics Exec. Director, Medical Affairs, Program Development/Education

Travis Mickle *KemPharm* President, CEO & Co-Founder

Sincerely,

Anthony Soscia

Atlantic Pharmaceuticals President

Sandra Stimson National Council of Certified Dementia Practicioners & International Council of Certified Dementia Practitioners Founder and CEO

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September 27, 2016

Steven D. Pearson, MD, MSc, FRCP President Institute for Clinical and Economic Review Two Liberty Square, Ninth Floor Boston, MA 02109

RE: ICER Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Dear Dr. Pearson:

The Academy of Managed Care Pharmacy (AMCP) thanks the Institute of Clinical and Economic Review (ICER) for the opportunity to provide comments on the draft scoping document that will examine the clinical effectiveness and value of abuse-deterrent formulation (ADF) of opioids in pain management released on September 8, 2016. AMCP appreciates the broad input from payers as well as patients, pain management specialists, and pharmaceutical manufacturers. ADFs present a management challenge for health care decision makers, including managed care organizations (MCOs), health plans, and other payers because of the lack of evidence regarding their effectiveness. AMCP applauds ICER in undertaking this challenging but valuable assessment of ADFs and believes that it is an important component in helping pharmacists, physicians, and nurses in MCOs and other health care decision makers critically evaluate ADFs to effectively manage the use of opioids in a clinically appropriate manner.

AMCP is a professional association of pharmacists and other practitioners who serve society by the application of sound medication management principles and strategies to improve health care for all. The Academy's 8,000 members develop and provide a diversified range of clinical, educational, medication and business management services and strategies on behalf of the more than 200 million Americans covered by a managed care pharmacy benefit.

Opioid analgesics have proven to be very effective in controlling short and long-term pain due to a large number of causes. These drugs are also the most commonly abused medications in the United States, reaching epidemic levels. AMCP is concerned both about the proper management of patients suffering from uncontrolled pain, as well as limiting abuse and diversion of opioids because the improper use of opioids carries enormous costs to our society that go beyond traditional health care costs. Pharmacists,

100 North Pitt Street | Suite 400 Alexandria, VA 22314 800 827 2627 | 703 683 8416 Fax 703 683 8417 www.amcp.org physicians, and nurses who work in managed care organizations have a responsibility to implement medication management programs and services to ensure appropriate use of opioids in the populations they serve and to work with other health care providers, patients, and caregivers to reduce the potential for misuse, abuse, or overdose of opioids.

Managed care organizations must carefully balance the unique and varied needs of patients who are taking these medications against the probability of abuse and diversion. Therefore, AMCP supports the ability of health plans, pharmacy benefit managers (PBMs), accountable care organizations, and integrated delivery systems to use managed care tools to effectively manage the use of opioids in a clinically appropriate manner. The use of frameworks is one potential resource to help make these determinations.

AMCP appreciates the thoughtful approach described under the analytic framework and believes the population of focus, interventions, and comparators outlined are appropriate. AMCP supports the breakdown of the populations that distinguishes therapeutic and non-therapeutic use of opioids; recreational users; and, opioid addicts because often this type of specificity is not always readily available in reviewing data. Generally reviews are based upon use of opioids in cancer and non-cancer patients.

AMCP supports the use of real world evidence on outcomes associated with specific opioids. This review should include analysis of payer data supplementary to conducting a systematic literature review and collecting other data. The payer information and the systematic literature review could help payers and other decision makers to make informed coverage determinations for ADFs and help to inform whether legislative and regulatory coverage mandates are consistent with existing evidence.

AMCP suggests that the economic evaluation and modeling used to determine the cost-effectiveness of ADFs should be made available to managed care pharmacists and other health care providers to facilitate to downloading, auditing, and testing the models by modifying the assumptions of the model based on their perspectives and their covered populations.¹ This could also allow for health care providers and decision makers to modify the assumptions of the model based on their perspectives and their covered populations. Health economic analyses would also be fully disclosed, meaning that bibliography, supporting documents, limitations, and potential biases would be fully detailed. Specifically, the availability of the economic models would, at minimum, allow for the following:

- Realistic adoption rates that accurately reflect the anticipated uptake of ADFs based on state legislation;
- Consideration of an appropriate quality-adjusted life year (QALY) threshold after consultation with available literature or an organization's bioethics committee;
- Adjustment of the cost of a medication to more accurately represent the actual net cost;

¹<u>AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data</u>. Journal of Managed Care & Specialty Pharmacy 2016 22:7, 826-831

- Flexibility to extrapolate the data for a short-term versus long-term forecast to better understand the immediate budget impact versus overall value of ADFs;
- Adaptability for factors such as emergency department, hospital utilization, or medication addiction treatments; and
- Validation that the economic model is applicable to the relevant patient population.

AMCP appreciates your consideration of the concerns outlined above and looks forward to continuing work on these issues with ICER. If you have any questions regarding AMCP's comments or would like further information, please contact me at 703-683-8416 or scantrell@amcp.org.

Sincerely,

TAUTA

Susan A. Cantrell. RPh, CAE Chief Executive Officer

VIA ELECTRONIC DELIVERY

September 28, 2016

Institute for Clinical and Economic Review Two Liberty Square, 9th Floor Boston, Massachusetts 02109

Re: Comments on Institute for Clinical and Economic Review (ICER) Draft Scoping Document on Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Dear ICER Review Team,

Thank you for the opportunity to comment on the draft scoping document on "Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value" (herein "Document"). Collegium Pharmaceutical, Inc. (herein "Collegium") is a specialty pharmaceutical company that manufactures and markets Xtampza[®] ER, an extended-release (ER) abuse-deterrent formulation (ADF) containing oxycodone as its active moiety.

Collegium commends the ICER Review Team for generating the Document that acknowledges the complexities of this review and the potential lack of required data. While Collegium agrees with many of the points made in the Document, there are a few that are deserving of further clarification or of an alternative point of view:

- The Document states that the most common form of abuse is "swallowing a number of intact capsules or tablets to achieve a feeling of euphoria" and it suggests that current abuse-deterrent technologies do not mitigate this risk. Collegium does not deny that oral administration is the most common form of abuse or that current ADFs do not prevent against abuse of intact tablets/capsules, however, oral abuse also encompasses manipulation of tablets/capsules. It has been well documented that the vast majority of prescription opioid abusers start by oral ingestion of intact tablets/capsules and then progress to oral administration of crushed or chewed tablets/capsule contents, eventually moving to abuse via alternate routes of administration (i.e., insufflation, inhalation, and intravenous) [1]. Furthermore, as the route of administration changes, the frequency of use and daily dose may increase, which is likely to accelerate the progression to addiction [2-4]. Xtampza ER has properties that protect against dose dumping following manipulations such as crushing, chewing, grinding, dissolving, or extracting, which could help to prevent the progression of abuse and have an impact on cost to Payors.
- The Document states that ICER will evaluate a range of evidence including "public health effects, reduction in disparities, innovation, and patient experience". Collegium agrees that it is critical to evaluate evidence that is not captured within standard clinical trials, however public health effect and patient experience data are not available at this point for the majority of currently marketed ADFs or those in development. Collegium seeks clarification on how ICER plans to evaluate this evidence, additionally Collegium asks that a definition of "disparities" be provided in the final scoping document.

- In the "Scope of Assessment" section, ICER states that their evidence review will include a number of stakeholders. Collegium agrees that it is critical that ICER review data from these sources. Collegium would also recommend that ICER include recreational drug abusers and addicts in this list, particularly those who can evaluate the street value (i.e., street price or anticipated street price for products in development) of different ADF products (<u>www.StreetRx.com</u>). This suggestion is in line with recommendations by FDA on epidemiologic studies [5].
- The Document describes plans to use a time-series analysis method (i.e., pre-ADF, post-ADF), however, Collegium would like to point out that this type of analysis can only be applicable for one ADF, OxyContin, and will not be possible for Xtampza ER or any other ADFs on market or in development. Collegium would seek clarification on how ICER plans to approach this analysis in the final scoping document.
- In Figure 1, Adverse Impacts box ICER lists the following points: "(1) diminished effectiveness of opioid for pain relief, (2) diminished access of patients to medication, and (3) increase in opioid use (false sense of security)". Collegium seeks further clarification on each of these points:
 - 1. How will ICER assess potential diminished effectiveness of opioid pain relief in their analysis? Standardized effect sizes for approved ADF versus non-ADF products are comparable across published Phase III trials [6-9] especially given the observation of increasing placebo responses over time in US clinical trials [10].
 - 2. Diminished patient access to medication is a function of coverage. Collegium would like to point out that a premature analysis of data that are non-existent or incomplete by ICER could have dire adverse consequences in this regard.
 - 3. Collegium would ask that ICER provide a description on how "false sense of security" will be defined and quantified and then associated with an increase in opioid use. Collegium would like to point out that there are 7 approved ADF opioids Targiniq ER is missing from the list. Additionally, Rexista ER (investigational) should be added to the list of ADFs.
- Collegium would seek for ICER to expand upon the comparators it plans to use for the analysis. Collegium would also stress the importance of selecting the correct comparator for each specific analysis. Using an IR comparator of the same moiety is appropriate for the evaluation of assay sensitivity as well as best case scenario for abuse (i.e., an IR will achieve the desired pharmacokinetic profile sought be recreational drug abusers and addicts) it will not give a complete overview of the situation [5]. An ADF comparator is also appropriate where data is available.
- Collegium shares ICER's interest in 'real world impact' as an outcome measure. However, this outcome is predicated on appropriate postmarketing exposure; to date, these data are only available for one ADF - OxyContin.
- ICER proposes to use the QALY to model the estimated cost-effectiveness of ADFs. Collegium would like to point out that the QALY analysis has been agressively criticized by many as not applicable to this US-based pharmacoeconomic endeavor as well as Congress' publicly stated disagreement on the use of the QALY. Collegium would urge ICER to reconsider using the QALY for this analysis.

General Comments:

In addition to the specific comments on the Document, Collegium would also like to stress that not all ADFs are equal. There are significant differences between marketed ADFs in labeling and the level of *in vitro*, pharmacokinetic, and clinical abuse potential data provided by Sponsors to the FDA. Collegium would ask that ICER include either a justification for an analysis that groups all ADFs together or to provide an approach for evaluating individual ADFs. As ICER has acknowledged, the FDA aims to convert the opioid market to only formulations with abuse-deterrent properties [11]. In addition to Massachuscetts and Maine, West Virginia and Florida have also passed legislation requiring Payors to cover ADF opioids. Additionally, four states have passed study resolution bills (Delaware, New Hampshire, Oklahoma, and Virginia) and another 30 bills related to ADFs in 20 more states are being considered during the 2016 session with more states likely to follow [12]. For this reason, Collegium thinks it is critical that ICER at least begin forming the framework for an eventual head-to-head comparision between ADFs as it is likely that this analysis will be the most useful moving foward.

Collegium urges ICER to carefully consider the consequence of any study conclusions, which may result in payors limiting ADF usage to failures of less expensive ER opioids. This could have the perverse effect of worsening the opioid addiction crisis by continuing to flood medicine cabinets with easy to abuse opioids when the goal should be to urgently reverse this practice.

Collegium urges ICER to consider that the FDA is requiring sponsors of ADF opioids to assess long-term population data to help determine the true value of ADFs on the market. These considerations relate to reducing abuse, misuse, and addiction in order to obtain epidemiological based abuse-deterrent labeling. Industry partners, including Collegium, are taking these studies very seriously and are presently collaborating with the FDA on study methodologies.

Conclusions:

Collegium recognizes the incredible importance of the analysis proposed by ICER in the Document. However, given the paucity of needed data, Collegium suggests that ICER sets a meeting with FDA and combines their efforts with the FDA to produce a scientifically rigorous, data-drive, truly useful analysis.

Thank you for allowing Collegium to offer its views as it pertains to ICER's Draft Scoping Document. Please feel free to contact us directly to discuss this review in greater detail.

Sincerely,

Timothy E. Hermes Vice President, Government Affairs Collegium Pharmaceutical (615) 812-9193 <u>thermes@collegiumpharma.com</u>

References:

- 1. Hays, L., *A profile of OxyContin addiction*. J Addict Dis, 2004. **23**: p. 1-9.
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September 28, 2016

Dear ICER Review Team:

I am writing on behalf of Egalet Corporation in regard to the Institute for Clinical and Economic Review (ICER) Draft Background and Scope document for Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value, dated September 8, 2016. Egalet is a fully integrated specialty pharmaceutical company focused on developing, manufacturing and commercializing innovative treatments for pain and other conditions. We are active in the field of abuse-deterrent opioid development and would like to share our perspectives for your consideration during the review process.

First, we were pleased to learn that the planned review will include Egalet's abuse-deterrent, extended-release morphine product candidate, ARYMOTM ER. ARYMO ER was developed for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. ARYMO ER uses Egalet's proprietary GuardianTM Technology, a polymer matrix tablet technology, which is combined with a novel application of injection molding for the manufacturing of pharmaceutical tablets. This results in tablets with controlled-release properties as well as physical and chemical features that have been demonstrated to resist both common and rigorous methods of manipulation, in order to deter common routes of abuse. The new drug application (NDA) for ARYMO ER is currently under review by the U.S. Food and Drug Administration (FDA) and its Prescription Drug User Fee Act (PDUFA) goal date for a decision is October 14, 2016.

The public health crisis of opioid misuse and abuse is an extremely complex issue which requires the participation of multiple stakeholders in order for progress to be made. The *FDA Opioid Action Plan* recognizes the importance of a balance between access to effective medications for patients living with pain while limiting the broader societal burden of opioid misuse and abuse. ¹ This paradigm alone changes the evaluation regarding the role of a specific class of therapy, and its value proposition, from a traditional model which focuses on the intended patient population to a broader assessment of how abuse-deterrent opioids can positively impact the broader community, within which pain patients receiving their medications live. This is because approximately 70% of opioids that are misused or abused originate from a legitimate prescription for a family member or friend that gets diverted out into the community.²

The understanding of the natural history of prescription opioid misuse and abuse is evolving. The current hypothesis is that the problem progresses along a continuum in susceptible individuals, sometimes starting with oral abuse of multiple intact tablets, followed by manipulated oral abuse, for which the most common mechanism of manipulation is chewing. While it is recognized that no abuse-deterrent technology to date addresses the issue of ingesting multiple intact tablets, chewing opioid tablets occurs both intentionally and unintentionally and results in faster release of the drug which leads to a more rewarding experience. The 'abuse cascade' can then progress to physical and



chemical manipulation of tablets utilizing various tools followed by oral, intranasal or IV administration. While overdose is a risk for all routes of abuse, intranasal and IV routes pose additional safety risks, such as infectious complications like HIV and hepatitis ³

As stated in the FDA Guidance for Industry *Abuse-Deterrent Opioids – Evaluation and Labeling* (April 2015), the goal of an abuse-deterrent opioid product is to make it less attractive and/or less rewarding to an abuser compared to a non-abuse-deterrent version of that opioid.⁴ These outcomes are based on two parameters: how difficult is it to manipulate or defeat a product to get it into an abuseable form; and, after that effort, how much is the product 'liked' once administered compared to a non-abuse-deterrent version of that opioid moiety? If a tablet can be easily crushed in seconds and snorted, or mixed into solution and prepared for IV injection, an abuser will seek out this kind of product for the ease of use and the yield of the active ingredient. By design, abuse-deterrent opioid products make it more difficult for an abuser to defeat a product and/or make the output of that effort less rewarding such that these technologies make abuse-deterrent products less desirable.

The FDA Abuse-Deterrent Opioid Guidance is also the road map for how to conduct pre-marketing abuse-deterrent studies (Categories 1, 2, & 3) in order to generate the data and level of evidence required to obtain abuse-deterrent label claims. Given that abuse-deterrent opioids have been commercially available for a limited number of years, and have limited market penetration, there is currently only a small amount of post-marketing data available to address the issue of clinical effectiveness in the real world. This scenario is common to all new classes of drugs, which are initially approved based solely on Phase 3 efficacy and safety data centered around narrow clinical endpoints and little, if any, outcomes data. A case in point is the statin class of medications; they were initially approved based on Phase 3 clinical endpoints of lowering both total and LDL cholesterol. It was not until about a decade later that the real-world clinical effectiveness data which demonstrated the broader value of statins in reducing the risk of cardiovascular events was reported and factored into the value proposition of this class of medications. Therefore, at the current time, Category 1, 2, and 3 abuse-deterrent data which makes up the level of evidence required by the FDA to obtain abuse-deterrent label claims, should be used by ICER and considered adequate for its review until more post-marketing real world data becomes available.

Opioid abuse and addiction is a chronic disease. In medicine, chronic illnesses are approached not only from an acute treatment perspective, but also importantly from a preventive perspective. Most of the discussion, and funding, around the management of opioid abuse, such as the use of naloxone by first responders for overdoses and the call for more medication-assisted treatment programs for addiction, has focused on acute intervention once the problem of opioid use disorder has already developed. Preventive approaches, as in the example of statins above, have been shown in several therapeutic areas to be more cost effective by limiting morbidity and mortality through early intervention, rather than managing the complications of a chronic condition. It is acknowledged



that abuse-deterrent opioid products are not 'abuse proof'; however, they represent a clear advancement over non-abuse-deterrent products and must be an integral component of a comprehensive prescription opioid misuse and abuse prevention plan, designed to limit harm for both patients and abusers and their associated family and friends.

A recent comprehensive review of the clinical and economic burden of abuse of prescription opioid analgesics in the US found individuals who abused prescription opioid analgesics were more likely than non-abusers to utilize medical services, such as emergency department visits, physician outpatient visits and inpatient hospital stays.⁵ A budget-impact model was developed and published in 2009 to assess potential cost savings from the introduction of an abuse-deterrent opioid to third-party payers. ⁶ The authors concluded that potential cost savings from introducing an abuse-deterrent opioid formulation that was specifically designed to resist or deter common methods of abuse, including injection, crushing, snorting and chewing for the US (assuming a privately insured cost structure) could range from approximately \$0.6 billion to \$1.6 billion per year depending on different scenarios. The societal cost savings associated with reductions in abuse would be expected to increase over time as more abuse-deterrent opioid products are introduced.

The field of abuse-deterrent opioids is relatively new and as such, the real world outcomes and economic data ICER desires may be limited. We encourage ICER not to view this as a limitation during its review of abuse-deterrent opioids, which could have a chilling effect on their uptake, and delay the acquisition of real-world abuse-deterrent outcomes information. To impact the opioid abuse epidemic now, it is imperative that we not wait for the "perfect" answer, but rather move forward with the available technologies, provide access to approved ADF products, and support the concept of incremental improvement.

As noted earlier, the *FDA Opioid Action Plan* recognizes the importance of a balance between access to effective medications for patients living with pain while limiting the broader societal burden of opioid misuse and abuse. Abuse-deterrent opioids can play an important role in helping to achieve this balance as one part of a multi-faceted approach to address this public health crisis. We appreciate the opportunity to share our perspectives and ICER's timely attention to this important topic.

Sincerely,

Layer, nD

Jeffrey M. Dayno, MD Chief Medical Officer Egalet Corporation



References:

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- Substance Abuse and Mental Health Services Administration: Results From the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: US Department of Health and Human Services; 2014. HHS Publication No. (SMA) 14-4863.
- 3. Meyer R, Patel AM, Rattana SK, et al. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul Health Manag.2014;17:372–387.
- 4. Food and Drug Administration (FDA). Guidance for Industry: Abuse-Deterrent Opioids Evaluation and Labeling. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research; 2015.
- 5. Meyer R, Patel AM, Rattana SK, et al. Prescription opioid abuse: a literature review of the clinical and economic burden in the United States. Popul Health Manag.2014;17:372–387.
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It's a disgrace to the American community suffering from severe chronic pain, then you leave us battling every second of every minute of every day of every week, and so on! If you truly know anything about pain, and I would think you do, you would have had to of known the level of distress & debilitating pain you would've unnecessarily left us severe chronic pain patients! So it sickens me more to know that you would be so careless NOT to have had a game plan so NOT to break the 1st rule of medicine "You Shall Do No Harm!" You did, you have gravely affected severe chronic pain patients by allowing DEA agents to threaten medical specialists who are board certified with their MEDICAL licenses and arrest if they do not "comply" with YOUR "recommendations!" We severe chronic pain patients have been profiled, defamed, forced to release personal medical information to try & fight against an unlawful act taken by Government entities! Doctors told DEA agents about chronic pain patients and their answers were, "So what, who cares!" Really, that's how you people see us severe chronic pain patients? We are drug tested, we've been counseled, we sign contracts, and agree to purchase from only ONE Pharmacy and some/most/ME has NO POLICE RECORD OR ISSUES WITH ADDICTION! All I have are 12 disc herniations – 5 or more are compressing my Spinal cord in the thoracic and NO ONE WILL OPERATE, SO IT'S NEVER BEEN TREATED BY THERAPY OR SURGERY - carpal tunnel in both wrists (was a chef), rest of herniations are in neck, thoracic & lumbar with neck fusion and L5-S1 laminectomy discectomy and ambulate with a cane due to sciatica pain and axon damage. I am all screwed up and you people forced my doctor against his professional opinion as "MY" pain specialist physician that I've been with for years to reduce the same medication that I've been taking for a while by 73%! Now you know people build up a tolerance but you decided not to take that into account. Why would all you people act this way, with such disregard for American citizens who are suffering with debilitating documented chronic pain and injuries? Have you ever suffered from pain? If yes, try living with that severe pain every second of every day with trouble sleeping, anxiety, depression sets in after all of that! Do you even know or care about that? Then all of the harm you have inflicted on us leads us to suffer from post-traumatic disorder due to lack of pain relief, quality of life, little sleep, withdrawal from society etc.... So basically we spiral downward and all of the progress made throughout the 15+ years are all but gone! Please rethink your devastating decisions that led to horrific consequences for millions of Americans! We are not the bad people, we follow the rules/laws and we just want to have some semblance of life because WE did not ask to be injured, disabled, sick, etc.....

Signed: Roberto Flores (Patient)



Relief from pain is important to millions of individuals who suffer from chronic illness. While prescription drugs such as opioids have proven a valuable tool in the relief process, the potential for abuse of opioids presents a very real and significant risk. As we are all aware, the misuse and abuse of opioids has reached epidemic levels across our nation.

Prescription drug abuse is the fastest growing drug problem in America – one that does not discriminate by region, socioeconomic status, or age. The Centers for Disease Control and Prevention have identified prescription drug abuse as an epidemic reporting more than 15,500 Americans deaths each year from prescription painkillers. An important step in the abuse prevention process for both new and chronic pain sufferer's is the development of tamper-resistant formulas for opiates. This development maintains access to these much needed medications and strongly minimizes the abuse potential.

The National Association of Drug Diversion Investigators, or NADDI, is a non-profit membership organization that works to develop and implement solutions to the problem of prescription drug abuse and diversion. NADDI advocates for the responsible use of prescription drugs by people who need them, and at the same time, aggressively works with law enforcement and regulators to pursue those involved in related criminal activity. Our primary focus is training and education for our members, which include law enforcement personnel, regulatory agents, health professionals, health care fraud investigators and pharmaceutical companies.

Continuing progress in the field of pain management involves a juggling act that balances the needs and interests of those involved. The development process involves all the stakeholders in the medical treatment of pain—clinical, legal, and regulatory, law enforcement, and industry, commercial, personal, and societal. NADDI recognizes that no one approach to maintaining this critical balance will succeed unilaterally. Therefore, NADDI supports ongoing interaction and cooperation among all who can impact the access to and provision of competent health care, and who can affect diversion and abuse of medications.

The development of abuse deterrent formulations is a scientific approach being taken to reduce illegal street activity of opioid medications. In speaking with and surveying our NADDI law enforcement members at trainings throughout the country, it appears that the rates of diversion of specific opioid medications decreased dramatically after the introduction of reformulated opiates.

2014 NADDI Members Survey Over 240 Responses Since the Reformulation of OxyContin in 2010 Prices have fallen significantly OxyContin is significantly less in demand Central Florida HIDTA OxyContin Pills Seized 2010-2014

2010 – 49,673 2011 – 26,959 – Florida PDMP went live 2012 – 1,070 2013 - 393 2014 – 127 99.6% Decrease in OxyContin Seizures

Pinellas County Sheriff's Office / OxyContin Pill Purchases 2010 – 134 2011 – 57 – Florida PDMP went live 2012 -13 2013 – 60 2014 – 0 2010-2014 Oxycodone purchases were at an all-time high

Pharmacy Robberies Rx Patrol – Nationwide database Prior to the reformulation of OxyContin OxyContin was demanded in 66% of Robberies After the reformulation - The demand dropped by almost 50%

Law enforcement have experienced a substantial decrease in seizures and undercover narcotics purchases of the OxyContin product during the last several years following the reformulation of this drug.

I would like to draw your attention to a May 11, 2016 op-ed from the Gaston Gazette covering Gaston county NC and surrounding communities.

"Over the past decade, dealing with skyrocketing rates of prescription drug abuse has become inevitable for those of us on the front lines in law enforcement. Just recently, a new report identified four North Carolina cities among the top 25 worst cities for drug abuse in the county. Hickory ranked fifth on this list.

"A common form of prescription drug abuse is when an abuser alters a prescription pain pill, via methods like crushing the pill into a powder to snort or smoke, or heating water and melting the tablets into a liquid to inject.

"Fortunately, there is a medical technology called OADP—opioids with abuse deterrentproperties—a reformulation of prescription opioid pills with chemical and physical barriers that make it more difficult to manipulate the pill for abuse purposes.

"According to a study, since the reformulation of prescription opioids with abuse-deterrent formulations, there have been significant reductions in the abuse of these prescription medications and a 50 percent reduction in drug misuse.

"Prescription drug abuse relentlessly and indiscriminately targets the intersections of the communities we as members of the law enforcement community try to protect every day.

North Carolina's lawmakers should adopt legislation—like House Bill 1048—that will reduce barriers to prescribing abuse-deterrent prescription opioids. The availability of abuse-deterrents will help save more lives and equip law enforcement in order to further protect the communities they serve."

Judy Billings

Judy Billings is president of the NC chapter of National Association of Drug Diversion Investigators of the Carolinas. She is employed in the NC SBI Diversion and Environmental Crimes Unit.

Adding new physical and chemical features to prescription opioids to deter abuse could also reduce misuse of these drugs and the sometimes deadly consequences. These products can be part of a comprehensive approach which should include prevention, interdiction, prosecution and substance-abuse treatment.

While the first generation of abuse deterrent formulations have reduced diversion, any advances in this technology that would further erode the street value of opioids and maintain access to the individuals who benefit from their relief would be welcomed.

Due to the ongoing problems with pharmaceutical drug abuse and diversion in the United States, NADDI is a strong proponent of new abuse deterrent medicines that make it more difficult for an abuser and reduce law enforcement involvement in healthcare. NADDI has a strong belief that the illegal diversion of prescription medication has a direct negative impact on legitimate patients, the vast majority who use controlled substances.

Sincerely,

/s/ Charles F. Cichon Executive Director <u>www.naddi.org</u> Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

RE: Comment on Draft Scoping Document

The scope should be expanded to include independent testing/reporting of abuse-deterrent formulations using protocols relevant to abuse. For example, extraction studies should be conducted using a matrix of particle size, agitation, temperature and solvent based on the properties of the formulation. Physical strength for abuse-deterrent formulations should be tested and reported using cutting force rather than breaking pressure. The current FDA-approved abuse-deterrent formulations are easily extracted using commonly available tools and solvents to high purity and high label claim by unskilled individuals in short periods of time. The scientific evidence must include independent testing in addition to the data submitted by the sponsor of the formulation. This work is key in analyzing the effectiveness of abuse-deterrent drugs in preventing abuse. In the absence of independent evidence for abuse deterrence properties, no impartial, clinical and public health relevant outcomes can be established—preventing measuring and linking causally to the intervention, which would likely produce biased and/or incomplete conclusions.

The protocols and results of clinical liking studies should be objectively evaluated for their ability to meet the standards of scientific evidence. The regulatory framework for producing substantial evidence of efficacy for abuse-deterrent properties should also be applied. Prospectively, the studies should assure that they can produce adequate and well-controlled, statistically significant, reproducible, with clinically meaningful results. The liking study protocols used in the FDA abuse-deterrent labeled products do not meet this standard and should not be used to measure clinical and public health-relevant outcomes.

Since the Council will discuss different strategies for combating the prescription opioid crisis, the scope should also include an evaluation of the effectiveness of prescription opioids in the treatment of chronic pain. The recent publication of the "CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016" and CDC Director Dr. Thomas Freiden's submission to the New England Journal of Medicine "Reducing the Risks of Relief—The CDC Opioid-Prescribing Guideline" should be provided to the Council as evidence that prescription opioids do not have substantial evidence of efficacy in the treatment of chronic pain, outside of the context of active cancer treatment or palliative or end-of-life care.

Edwin R. Thompson

President



September 23, 2016

Steven D. Pearson, MD, MSc, FRCP President Institute for Clinical and Economic Review One State Street, Suite 1050 Boston, Massachusetts 02109

Re: Call for Comment - Draft Background and Scope for Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Dear Dr. Pearson,

As a pioneer and leader in the development of abuse-deterrent technologies, Purdue Pharma L.P. welcomes the opportunity to submit comments regarding the scope of the ICER review: Abuse-Deterrent Formulation of Opioids in Pain Management.

First, we would like to commend ICER for recognizing the importance of "*evaluating evidence that is not typically captured in the clinical trials, including public health effects, reduction in disparities, innovation and patient experience.*"¹ Purdue's initial comment letter focused on these areas, and we continue to believe the following are critical to determining value in this area:

- <u>Put patients first and take a societal perspective</u> in order to understand the broader value of opioids with abuse-deterrent properties (OADP). ICER highlighted the importance of both patient and societal perspectives in this therapeutic area, acknowledging that the value of these products will be measured not only by clinical effectiveness (reduction in diagnoses of abuse/dependence, overdose and death) but also by their potential to affect abuse or misuse in the community (eg, diversion and street price).
- <u>Use the revised, though not yet final, ICER Value Assessment Framework in this review</u>, specifically because it intends to better account for methods to integrate the "*contextual considerations*" and "*additional benefits and disadvantages*" that are critical to conducting an accurate assessment of OADP value. While not stated, the draft scoping document emphasizes these considerations and appears to be following the intent of a revised framework. The value of OADP must be assessed beyond the direct effects on commercial health plan costs that can be captured in a traditional budget impact model, and we applaud ICER for implementing these enhancements and using its improved Value Assessment Framework in this review.
- Follow the FDA Guidance on Abuse-Deterrent Opioids. While we continue to assert that the FDA must be the final evaluator and arbiter of labeling resulting from category 4 studies (ie, evidence of real-world effectiveness), we were very encouraged that ICER emphasized the

importance of real-world, pre-/post-reformulation time series data as evidence of that effectiveness. We are, however, concerned that ICER appears to be almost completely discounting category 3 data, evidence of "*Clinical Abuse Potential*." We ask that ICER reconsider this position, and accept real-world evidence of reduced abuse and its sequelae as confirming the predictive validity of category 3 data.

• <u>Use real world data and established economic principles</u>. The US opioid market is mature, and all data show that the market is shrinking at an increasing rate, despite the launch of several new medicines, which have taken share primarily from other branded products. A budget impact model should reflect these realities to avoid exaggerated and unrealistic market growth projections.

We offer the following comments regarding the review criteria and analytic framework for consideration as ICER finalizes the scope for this review:

- Populations:
 - *Cancer pain:* In addition to patients suffering from chronic skeletal-muscular pain, we note that patients with cancer pain are included within the scope of this review. Although many studies have excluded patients with cancer pain, this is a valid population relevant to opioids with abuse-deterrent properties, especially in light of potential diversion of current or leftover medications. Here, it is critical to take the greater societal perspective, ie, diversion of opioids from patients who are receiving/have received palliative care.
 - *Substance abusers*: We suggest, for this review of Abuse-Deterrent Formulation of Opioids in Pain Management, that "*persons addicted to opioids*" be revised to "*persons misusing and abusing prescription opioids*." Several studies have shown that a large percentage of heroin users have also misused a prescription opioid.^{2,3} However, a very large proportion of patients diagnosed with opioid use disorder also smoke tobacco and have other substance use histories (eg, alcohol, marijuana, benzodiazepines, or amphetamines).^{4,5} It is important that ICER does not make the same false attribution others have made by ignoring all other previous substance abuse or misuse and attributing all heroin use to previous prescription opioid use, or paradoxically to the introduction of OADPs.
- <u>Comparators</u>: The comparators of interest are listed as formulations of specific opioids without recognized abuse-deterrent properties, both in immediate-release (IR) and extended-release (ER) forms. Because there are no currently-available IR opioid formulations with FDA-approved abuse-deterrent properties, we are concerned that including IR drug products as comparators for specific opioids (or as a class) will conflate the value of extended-release with the value of abuse-deterrence, inappropriately biasing economic analyses, as the current non abuse-deterrent IR opioid market is dominated by generic products. The comparators, therefore, should be limited to ER opioid analgesic products, brand or generic.

- <u>Analytic Framework</u>: We applaud ICER for including real-world outcomes as well as those that are clinically relevant. We encourage ICER to provide additional detail in the final scoping document as to how policies related to opioid prescribing will be evaluated and incorporated, including both benefits and unintended adverse impacts to patients and society from reductions in medication access and obstructive coverage policies.
- <u>Economic Evaluations</u>: In addition to using realistic assumptions about market growth and share displacement, we ask that ICER incorporate a realistic view of drug pricing relative to OADP value. For example, when reformulated OxyContin[®] was launched, Purdue did not increase Red Book price or wholesale acquisition cost (WAC). The original Red Book price of OxyContin was based on the value of the extended-release formulation of oxycodone over immediate release. When the abuse deterrent reformulation was launched, there was no incremental price increase for the abuse-deterrent properties. Therefore, the abuse-deterrent formulation of OxyContin was introduced at the same Red Book price and WAC as the original formulation, meaning any decrease in abuse-related events and associated reimbursement must be considered cost saving by all standard economic principles.

In closing, thank you for the opportunity to provide input. Purdue will provide a bibliographic list of relevant clinical, epidemiologic, economic, and policy publications for consideration as follow-up to these comments and we look forward to a continued scientific engagement with ICER regarding this review.

Sincerely,

Tracy J. Mayne, PhD Head of Medical Affairs Strategic Research Purdue Pharma L.P

- Tracy mayne

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- 2. SAMHSA. CBHSQ Data Review: Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States. August 2013.
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- Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users – United States, 2002-2013. MMWR Morb Mortal Wkly Rep 2015;64:719-25.
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ICER Evidence Package- Purdue bibliography

RANDOMIZED CONTROLLED TRIALS: ABUSE POTENTIAL STUDIES

OxyContin

1. Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. *J Clin Pharmacol*. 2014;54(4):468-477.

<u>Hysinlga ER</u>

- Harris S, Cipriano A, Colucci S, Kapil R, Geoffroy P, Hopyan T, Levy-Cooperman N. Oral Abuse Potential, Pharmacokinetics, and Safety of Once-Daily, Single-Entity, Extended-Release Hydrocodone (HYD) in Recreational Opioid Users. <u>Pain Med. 2016;17(5):820-31</u>.
- 3. Harris SC, Cipriano A, Colucci SV, Kapil RP, Geoffroy P, Hopyan T, Levy-Cooperman N. Intranasal Abuse Potential, Pharmacokinetics, and Safety of Once-Daily, Single-Entity, Extended-Release Hydrocodone (HYD) in Recreational Opioid Users. (HYD1014) *Pain Med.* 2016;17(5):820-31.
- Kapil RP, Cipriano A, Wen W, Lynch SY, He E, Colucci SV, Harris SC. Pharmacokinetic Profile and Sustained 24-hour Analgesia of a Once-daily Hydrocodone Bitartrate Extended-release Tablet with Abuse-deterrent Properties. (24 hour Dosing and Analgesia) <u>*Clin Ther.* 2016;38(2):302-314.</u>

EPIDEMIOLOGY: PRE-/POST-REFORMULATION TIME SERIES ANALYSES

Mortality

 Sessler NE, Downing JM, Kale H, Chilcoat HD, Baumgartner TF, Coplan PM. Reductions in reported deaths following the introduction of extended-release oxycodone (OxyContin) with an abuse-deterrent formulation. <u>Pharmacoepidemiol Drug Saf. 2014;23(12):1238-46.</u>

Overdose/Poisoning

- Stumbo SP, Yarborough BH, Janoff SL, Yarborough MT, McCarty D, Green CA. A Qualitative Analysis of Family Involvement in Prescribed Opioid Medication Monitoring among Individuals who have experienced Opioid Overdoses. <u>Sub Abuse</u>. 2016;37(1):96-103.
- LaRochelle MR, Zhang F, Ross-Degnan D, Wharam JF. Rates of Opioid Dispensing and Overdose After Introduction of Abuse-Deterrent Extended-Release Oxycodone and Withdrawal of Propoxyphene. <u>JAMA Intern Med. 2015;175(6):978-987</u>.

Misuse/Abuse

- 8. Dart RC, Surratt HL, Cicero TJ, Parrino MW, Severtson SG, Bucher-Bartelson B, Green JL. Trends in Opioid Analgesic Abuse and Mortality in the United States. <u>N Engl J Med. 2015;372(3):241-8</u>.
- Butler SF, Cassidy TA, Chilcoat H, Black RA, Landau C, Budman SH, Coplan PM. Abuse Rates and Routes of Administration of Reformulated Extended-Release Oxycodone: Initial Findings From a Sentinel Surveillance Sample of Individuals Assessed for Substance Abuse Treatment. <u>J Pain.</u> <u>2013;14(4)351-8.</u>
- Cicero TJ, Ellis MS, Surratt HL. Effect of Abuse-Deterrent Formulation of OxyContin. <u>N Engl J</u> <u>Med. 2012;367(2):187-189</u>.

EPIDEMIOLOGY: <u>Misuse/Abuse</u> (continued)

- 11. Coplan PM, Kale H, Sandstrom L, Landau CJ, Chilcoat HD. Changes in Oxycodone and Heroin Exposures in the National Poison Data System after Introduction of Extended-Release Oxycodone with Abuse-Deterrent Characteristics. <u>Pharmacoepidemiol Drug Saf.</u> <u>2013;22(12):1274-82</u>
- 12. Cicero TJ, Ellis MS. Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin. *JAMA Psychiatry*. 2015;72(5):424-30.
- 13. Cicero TJ, Ellis MS, Kasper ZA. Relative preferences in the abuse of immediate-release versus extended-release opioids in a sample of treatment-seeking opioid abusers. <u>Pharmacoepidemiol</u> <u>Drug Saf. 2016; epub ahead of print.</u>
- Severtson SG, Bartelson BB, Davis JM, Muñoz A, Schneider MF, Chilcoat H, Coplan PM, Surratt H, Dart RC. Reduced Abuse, Therapeutic Errors, and Diversion Following Reformulation of Extended-Release Oxycodone in 2010. <u>J Pain. 2013;14(10):1122-1130.</u>
- 15. Buer LM, Havens JR, Leukefeld C. Does the New Formulation of OxyContin[®] Deter Misuse? Qualitative Analysis. <u>Subst Use Misuse</u>. 2014;49(6):770-774.
- Sankey C, Setnik B, Harsanyi Z, Michalko K, Yang Z, Geoffroy P. Opioid use following the introduction of an extended-release oxycodone formulation with tamper-resistant properties: Prospective historical chart review in methadone-maintained patients. <u>J Opioid Manag.</u> <u>2016;12(2):149-59</u>.
- 17. Hwang CS, Chang HY, Alexander GC. Impact of abuse-deterrent OxyContin on prescription opioid utilization. *Pharmacoepidemiol Drug Saf.* 2015;24(2):197-204.

Switching at time of reformulation

18. Michna E, Kirson NY, Shei A, Birnbaum HG, Ben-Joseph R. Use of prescription opioids with abuse-deterrent technology to address opioid abuse. *Curr Med Res Opin* 2014; 30(8)1589-98.

Diversion

- Degenhardt L, Larance B, Bruno R, Lintzeris N, Ali R, Farrell M. Evaluating the Potential Impact of a Reformulated Version of Oxycodone Upon Tampering, Non-adherence and Diversion of Opioids: The National Opioid Medications Abuse Deterrence (NOMAD) Study Protocol. <u>Addiction. 2015;110(2):226-37</u>.
- Shei A, Rice JB, Kirson NY, Bodnar K, Birnbaum HG, Holly P, Ben-Joseph R. Sources of prescription opioids among diagnosed abusers. <u>*Current Medical Research &</u> <u>Opinion. 2015;31(4):779-784.</u>
 </u>*
- Doctor shopping
 - Chilcoat H, Coplan P, Harikrishnan V, Alexander L. Decreased diversion by doctor-shopping for a reformulated extended release oxycodone product (OxyContin). <u>Drug Alcohol</u> <u>Depend. 2016;165:221-8</u>

Comaprison between ADFs

 Cicero TJ, Ellis MS, Kasper ZA. A tale of 2 ADFs: differences in the effectiveness of abusedeterrent formulations of oxymorphone and oxycodone extended-release drugs. <u>Pain.</u> <u>2016;157(6):1232-8.</u>

EPIDEMIOLOGY (continued)

Internet monitoring

 McNaughton E, Coplan PM, Black RA, Weber SE, Chilcoat HD, Butler SF. Monitoring of Internet Forums to Evaluate Reactions to the Introduction of Reformulated OxyContin to Deter Abuse. <u>J</u> <u>Med Internet. Res 2014;16(5):e119.</u>

<u>Reviews</u>

- Coplan P, Chilcoat H, Butler SF, Sellers EM, Kadaki A, Harikrishnan V, Haddox JD, Dart RC. The Effect of an Abuse-Deterrent Opioid Formulation on Opioid Abuse-Related Outcomes in the Post-Marketing Setting. <u>*Clin Pharmacol Ther.*</u> 2016 [epub ahead of print].
- Havens JR, Leukefield CG, DeVeaugh-Geiss AM, Coplan P, Chilcoat HD. The Impact of a Reformulation of Extended-Release Oxycodone Designed to Deter Abuse in a Sample of Prescription Opioid Abusers. <u>Drug Alcohol Depend.</u> 2014;139:9-17.
- 25. Jones MR, Carney MJ, Kaye RJ, Prabhakar A, Kaye AD. Drug formulation advances in extendedrelease medications for pain control. <u>*Curr Pain Headache Rep.* 2016;20(6):36.</u>

Cost and economic analyses

Costs of abuse

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- Kirson NY, Shei A, Rice JB, Enloe CJ, Bodnar K, Birnbaum HG, Holly P, Ben-Joseph R. The burden of undiagnosed opioid abuse among commercially insured individuals. <u>*Pain Med.*</u> <u>2015;16(7):1325-32.</u>
- Shei A, Rice JB, Kirson NY, Bodnar K, Enloe CJ, Birnbaum HG, Holly P, Ben-Joseph R. Characteristics of high-cost patients diagnosed with opioid abuse. <u>J Manag Care Spec</u> <u>Pharm. 2015 Oct;21(10):902-12.</u>

Cost consequences of OxyContin reformulation

- 29. Canadian Agency for Drugs and Technologies in Health. Rapid Response Report: Summary with Critical Appraisal. *Tamper-Resistant Oxycodone: A review of the Clinical Evidence and Cost-effectiveness*. June 25, 2015. Available at <u>https://www.cadth.ca/tamper-resistant-oxycodone-review-clinical-evidence-and-cost-effectiveness</u>. Accessed September 20, 2016.
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- Rossiter LF, Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, Michna E. Medical cost savings associated with an extended-release opioid with abuse-deterrent technology in the US. <u>J</u> <u>Med Econ. 2014;17(4):279-87.</u>

32. Weingarten, W. Abuse deterrent opioids are worth the cost. Forbes. 2015, March 13. <u>http://www.forbes.com/sites/econostats/2015/03/13/abuse-deterrent-opioids-are-worth-the-cost-2/#18b8b9a83707</u> As a chronic pain patient, who has been and still is subjected to bias, excessive scrutiny, discrimination and prejudice simply for being a chronic pain patient that after exhausting all options, needs to take opioid pain relievers, I am a little wary of the ADF types of pain medications. First, when looking at the actual statistics actual, legitimate chronic pain patients do *not* historically have a high incidence of abuse, misuse, and addiction. Most of these incidents actually come from non-medical use by addicts without any pain related conditions.

Second, with the continuing sensationalism, and exaggeration of the current opioid 'epidemic', it could be possible that current formulations that still work as well as expected could be phased out and made out of reach by the average pain patient in favor of these newer formulations. In my opinion, there is no 'epidemic' within the actual, legitimate pain patient community and so there is no dire, immediate need for this formulation. However, in seeking profits, the manufacturers might try to force or coerce the prescribing of the newer formulations to a population that frankly doesn't need it. Add to this fact that this same population is mostly on a limited, and often fixed low income. The newer ones might still be out of reach, when the standard opioid pain relievers do just fine for them and they can afford it.

So the way I see it, these formulations should actually be used for verified, legitimate pain patients who HAVE a history of substance abuse or predisposition, and a familial history as well. Because they are the pain population that are actually 'at risk', not the average pain patient.

So to summarize my concerns are:

- 1. The possibility of an aggressive enforcement of current pain patients being forced onto these new "ABUSE" deterrent formulations, making it appear that the patient NEEDS an "ABUSE" deterrent because they will abuse, when there is no evidence and all the studies have consistently shown that actual, verified legitimate patients have a LOW incidence of abuse. It is 'reputation' harming as all medical professionals who read up on the patient's records will see this and then believe the patient HAS a 'drug abuse' disorder... else why would they prescribe an "ABUSE DETERRENT" formulation to this patient?
- 2. The typical patient is mostly on a limited and or fixed, low income. These ADF will more than likely have a high price tag, which in many cases, the insurer will pass to their higher cost Tier, making it a very expensive co pay. Which could mean, now MILLIONS of patients will literally not be able to afford their most effective treatment, their pain medicine.
- 3. Typically, pharmaceutical companies try aggressive tactics to encourage the prescriber to prescribe THEIR medicine, creating a dynamic of both Pharma and the prescriber forcing this low income patient, with historically no issue with abuse, HAVE to take that medicine or 'leave it'. Essentially holding the patient 'hostage' in a manner of speaking. The patient does not need an abuse deterrent formulation, it makes it appear they ARE an addict and 'at risk', they can't afford the newer ADF medicine, the doctor will not prescribe the tried and true, effective opioid pain medication that not only works fine and is affordable to the patient.

What kind of environment will be created, seeing the exaggeration, hysteria, and sensationalism we see with this so called 'opioid epidemic'?

4. With any abuse deterrent technology, the ingestion and absorption rates are often what are affected. What happens if, since certain medications like Oxycodone, for example,

don't actually have a high rate of absorption already, the medicinal component is NOT being absorbed FULLY? we can now see patients , who may have absorption issues already, ingesting a medication, that may cost double their usual copay, be even LESS effective. This is simply not acceptable. Again, oxycodone, for example, has a bioavailability of between 60 to 70 percent. To lower them even further can have serious impacts on health and wellbeing, not to mention efficacy factors for their pain management long term.

What guarantees does the patient have that:

- a. it will actually WORK and the medicine will be fully ABSORBED
- b. the patient will not receive even MORE stigma and discrimination
- c. the patient will be able to AFFORD the newer ADF
- d. the patient will have the option to GO BACK to their tried and true medications?
- e. the patient will *not* be COERCED and FORCED to go on this medication, given they have NO history of abuse in the past?

If you can address these issues, honestly and afford the consumers certain guarantees, perhaps their might be more acceptance by the pain patient community, and perhaps the medical professionals can operate with more transparency, and moral and ethical standards.

Thank you for reading this.

Sincerely, S.D.



September 27, 2016 Steven D. Pearson, MD, MSc, FRCP President Institute for Clinical and Economic Review

RE: Draft Background and Scope on Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Dear Dr. Pearson,

Thank you for the opportunity to review and comment on the aforementioned draft scoping document on Abuse-Deterrent Opioid Formulations (ADF). There are 5 major areas for which we have provided comments and input: Scope of the Proposed Assessment, Population of Interest, Interventions and Comparators, Clinical Outcomes, and Methodology.

Scope of the Proposed Assessment

1. The scope of ICER's evaluation aims to address and inform decision-making by patients, clinicians and policy-makers, within the context of multiple efforts being undertaken to combat the opioid crisis.

By definition this is a very broad mandate and the proposed methods attempt to cover all aspects and audiences together without sufficiently addressing any one perspective. It is strongly suggested that ICER clearly delineate each objective, the proposed methodology, and sources for each perspective. **Population of Interest**

1. In patients for who non-opioid pain management alternatives are ineffective, opioids may be a necessary option. It is crucial to safeguard this therapeutic option for appropriate use when indicated for the benefit of patients. Accordingly, the title of the ICER evaluation indicates a specific focus on Pain Management. However, the analytic framework describes inclusion of non-therapeutic opioid use. It is critical that the intended scope and operational definitions be clarified for transparency and to ensure the methodology is appropriately aligned.

Interventions and Comparators

1. Selection of interventions: It is not clear from the draft scoping document what the inclusion criteria are for intervention selection as not all ADF products (ie, in groups a, b, and c, below) are listed. Clarity is also requested on how ICER aims to evaluate products which have been approved but are not yet marketed and products which are still in development. For example, how does ICER plan to measure and evaluate the abuse deterrence of ADFs before and after introduction of an ADF for products that are in groups b and c below? Specifically, it is imperative that ICER clearly delineate these criteria as they pertain to products that are:

- a. Approved and marketed with an ADF label
- b. Approved with an ADF label, not yet marketed
- c. ADF in development
- 2. Selection of comparators: It is recommended that ICER provide details regarding selection of the non-ADF comparators (eg, generic vs branded) to ensure transparency in the scoping of this evaluation in terms of:
 - a. Route of administration oral, injectable or transdermal
 - b. Active ingredient similar to those of the ADFs?
 - c. Non-ADF extended-release formulations
 - d. Short acting formulations

Clinical Outcomes

- 1. ICER has provided insufficient detail in the scoping document on the outcomes of interest and how they align with the key research questions, which limits an adequate review and response. How does ICER plan to evaluate outcomes with respect to the FDA label categories and the separate routes for potential abuse (ie, oral, nasal, injectable)?
- 2. The draft scoping document notes that the clinical trial outcome "drug liking" (used as a proxy or indicator of abuse and often employed in ADF trials) has limited applicability or practical implications in evaluating clinical and policy implications associated with the use of ADF products. Drug liking, however, represents only one of the categories outlined in the FDA evaluation and labeling guidance to industry on ADF drugs which provides the basis for approval of this class of products¹⁻².
- 3. ICER has specified several other clinical outcomes of interest with limited detail on how these will be measured and applied. The lack of clarity of these raises many questions.
 - a. A clear delineation is needed for outcomes that specifically apply to persons using opioids for therapeutic use (eg, diminished pain relief, etc) and persons using opioids for non-therapeutic use (eg, diminished rate of diversion).
 - b. How will the periods before/after introduction of an ADF be measured for the population of patients who are using opioids for non-therapeutic purposes?
 - c. Please clarify how ICER will evaluate the impact of policies (health plan, state legislation, professional regulation) on outcomes of interest and which outcomes, specifically, are of interest for each stakeholder.

Method

1. To ensure that ICER employs scientifically rigorous methods and robust strategies to appropriately assess the weight of evidence, supporting the various interventions across unspecified follow-up periods (page 6 notes "any duration" will be considered), details regarding the methodological rigor planned for the comparative analyses are needed. For example, to-date, only 3 of the ADFs (Oxycontin ER, Hysingla ER, Embeda ER) identified by ICER have a follow-up of at least 1-year in post-marketing data that would permit the

specified pre-post evaluation of outcomes such as abuse-deterrence, with the others having none or less than 3 months of post-marketing data.

2. With the inclusion of observational studies, objective and operationalized definitions of outcomes are needed. While we acknowledge that the scoping document serves as an early outline of the research plan, additional clarity of key definitions is warranted to support informed and valuable stakeholder input during this critical phase. This includes, but is not limited to, "patient decision making," "cost to implement and use ADFs," "persons addicted to opioids" and "recreational drug users".

Once again, thank you for the opportunity to review this scoping document we look forward to having further discussions on the comments, including providing further clarity if needed.

Sincerely,

Kavita Gajria, B.S.Pharm, MS Director, Global HEOR on behalf of Teva Pharmaceuticals

References

 U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Abuse-deterrent opioids – evaluation and labeling guidance for industry.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm Accessed September 22, 2016.

2. Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. *N Engl J Med.* 2016;374(15):1480-1485.