June 16, 2020

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition pursuant to Title 21, Chapter 9, Subchapter V, Part A of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 10.30 to request that the Commissioner of the U.S. Food and Drug Administration (FDA) adopt language in the Black Box Warning and Package Insert for opioids that reflect the *HHS Guidance for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics* published in September of 2019 (copy attached).

ACTION REQUESTED

The Petitioner requests the FDA to:

1. Amend current black box warnings on all opioid analgesics to include:

   WARNING: In order to reduce the risk of addiction and death due to overdose, prescribers of opioid analgesics in patients who have achieved adequate pain control should seek the patient's cooperation with a program of gradual reduction in dosing and discontinuation if possible. ***(See Dosage and Administration General Principles)***

2. Require that package inserts for all opioids include the recommendation that patients with adequately controlled pain on a stable dose of opioids should be engaged by prescribers about their willingness to titrate down their daily dosage and ultimately discontinue opioids if possible (please see suggested insert for inclusion in section of package insert on Dosage and Administration General Principles).

STATEMENT OF GROUNDS

I. OVERVIEW

Overprescribing of prescription opioids is contributing to the opioid addiction epidemic of fatal overdose in the United States. In October 2019, Health and Human Services (HHS) published *A Guide for Clinicians on Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics.*

FDA guidance indicates that a black box warning is appropriate in several circumstances, including when[1]:

- "There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug;"

  OR

- "There is a serious adverse reaction that can be prevented or reduced in severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation)"

  Both conditions are met in this case.

Accordingly, we are petitioning the FDA to add to the existing black box warnings on all opioids a statement to strongly encourage prescribers to engage their pain patients whose pain is adequately controlled about tapering of the dose of opioid and ultimately, discontinuation of the opioid, if possible.

The rationale for this request and the approach to this risk mitigation is contained in the "HHS Guide for Clinicians on the Appropriate Dosage Reduction of Long-term Opioid Analgesics" published in September 2019.

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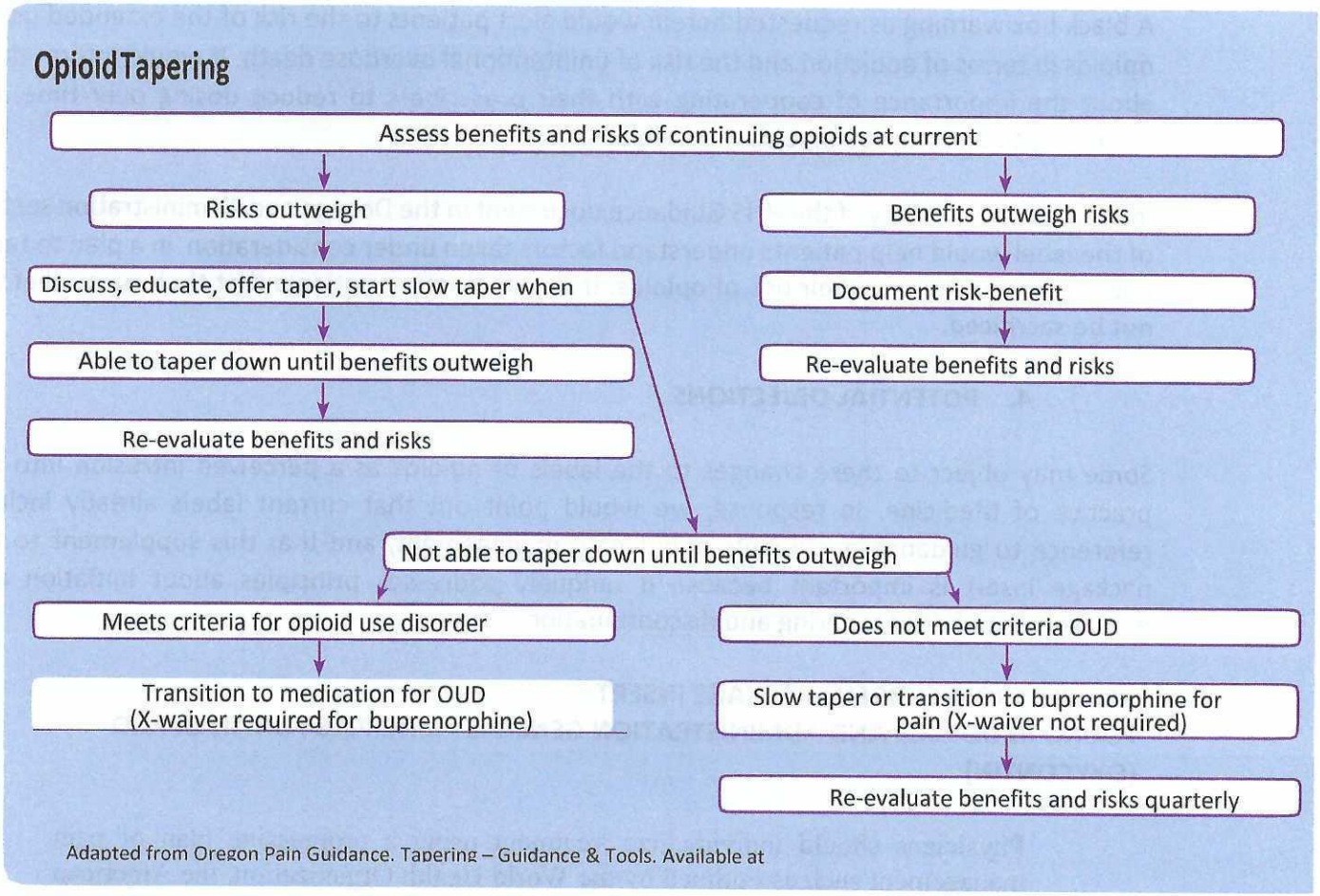
[1] Food and Drug Administration. "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Content and Format." 6 October 2011

2.SUGGESTED ADDITION TO PACKAGE INSERT SECTON ON DOSAGE AND ADMINISTRATION GENERAL PRINCIPLES



(Source: HHS Guide for Clinicians on the Appropriate Dosage Reduction of Long-Term Opioid Analgesics. Sept 2019)

Consider[iii] tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, when

- Pain improves[3,4]
- The patient receives treatment expected to improve pain[3]
- The patient requests dosage reduction or discontinuation[2,3,5]
- Pain and function are not meaningfully improved[2,3,5]
- The patient is receiving higher opioid doses without evidence of benefit from the higher dose[2,3]
- The patient has current evidence of opioid misuse[3,4,5]
- The patient experiences side effects[iv] that diminish quality of life or impair function[3,4,6]
- The patient experiences an overdose or other serious event (e.g., hospitalization, injury),[2,5] or has warning signs for an impending event such as confusion, sedation, or slurred speech[2,6]
- The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for adverse outcomes[3,5]
- The patient has been treated with opioids for a prolonged period (e.g., years), and current benefit-harm balance is unclear

3. PUBLIC EDUCATION

A black box warning as requested herein would alert patients to the risk of the extended use of opioids in terms of addiction and the risk of unintentional overdose death. It would inform them about the importance of cooperating with their prescribers to reduce dosing over time and ultimately to discontinue opioids if possible.

Inclusion of a summary of the HHS Guidance document in the Dosage and Administration section of the label would help patients understand factors taken under consideration in a plan to taper and possibly terminate their use of opioids. It would reassure patients that their pain relief will not be sacrificed.

4. POTENTIAL OBJECTIONS

Some may object to these changes to the labels of opioids as a perceived intrusion into the practice of Medicine. In response, we would point out that current labels already include reference to guidance documents about pain management, and that this supplement to the package insert is important because it uniquely addresses principles about initiation and management of dose tapering and discontinuation.

SAMPLE FROM CURRENT PACKAGE INSERT
FOUND IN DOSAGE AND ADMINISTRATION GENERAL PRINCIPLES FOR AN OPIOID (OXYCONTIN)

> Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring

5. FDA AUTHORITY

The Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Section 901(a) of the FDAAA added Section 505(o)(4) to the FDCA, granted FDA authority to mandate post- approval safety-related labeling changes for both individual drugs and classes of drugs.

ENVIRONMENTAL IMPACT

According 1921 CPR Sec. 25.31(a), this Petition qualifies for a categorical exclusion from the requirement that an environmental impact statement be submitted.

ECONOMIC IMPACT

According to 21 CPR See 10.30(b)~ an economic impact statement is to be submitted only when requested by the Commissioner following reviewing of this Petit

CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition that are unfavorable to the petition.

Francis E. O'Donnell, Jr., MD

(b) (6)

[redacted]