DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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APR 1 6 2014

National Advocates for Pregnant Women
15 West 36th Street, Suite 901
New York, NY 10018-7126

RE: Docket Nos. FDA-2013-P-1288 and FDA-2013-P-1289

Dear Petitioner:

This letter responds to your citizen petition, docket number FDA-2013-P-1288 (Citizen Petition), and petition for stay of action, docket number FDA-2013-P-1289 (Petition for Stay), both dated October 7, 2013 (collectively, Petitions). The Petitions collectively request that the Food and Drug Administration (FDA or Agency): (1) stay indefinitely the implementation of (*i.e.*, refrain from implementing), its neonatal opioid withdrawal syndrome (NOWS)-related safety labeling changes (SLCs) for extended-release/long-acting (ER/LA) opioid analgesics (Citizen Petition at 1-2; Petition for Stay at 1-2); (2) "remove the NOWS boxed warning" from ER/LA opioid analgesic labeling (Citizen Petition at 2); (3) "remove all references [in ER/LA opioid analgesic labeling] to NOWS as life-threatening, including in the patient counseling information and medication guide" (Citizen Petition at 2); and (4) present its NOWS-related issue-specific literature reviews to an Advisory Committee (Citizen Petition at 2). The Petitions further request that FDA: (1) include Petitioner-provided language regarding opioid substitution treatment (OST) in the full prescribing information of ER/LA opioid analgesic labeling (Citizen Petition at 2); and (2) replace section 5.3 of the Warnings and Precautions section of ER/LA opioid analgesic labeling with certain Petitioner-provided language (Citizen Petition at 2).

We have considered the Petitions carefully. For the reasons that follow, your requests are denied.

I. BACKGROUND

A. NOWS

NOWS is a constellation of signs and symptoms exhibited by neonates[1] born to women who have used or abused opioid drugs during pregnancy. Usually within the first 72 hours of life, infants with NOWS exhibit irritability with a high pitched cry, hyperactive primitive reflexes, hypertonicity, tremors, feeding difficulties, gastrointestinal disturbances and failure to thrive.[2,3]

[1] The term "neonate" generally refers to newborn infants up to 28 days old. For the purpose of this response, the term neonate, newborn, "baby," and infant will be used interchangeably.

[2] Jansson L and Valez M. Neonatal abstinence syndrome. *Curr Opin Pediatr* 2012; 24:252-258.

[3] Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31.

Severity of symptoms is typically determined by applying an assessment tool such as the Finnegan scoring system[4] or a modified version thereof. The infant is evaluated over time and if the score reaches a pre-specified cut-off point, the infant is considered to have severe symptoms.[5] Depending on symptom severity, treatment may range from comfort care (*e.g.*, swaddling, non-nutritive sucking) to administration of opioid-containing medications.[6] Further discussion of this condition occurs in section II, below.

B. NOWS Safety Labeling Changes for ER/LA Opioid Analgesics

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[7] authorizes FDA to require holders of approved drug applications to make SLCs if the Agency becomes aware of new safety information that FDA determines should be included in the labeling of the drug. *New safety information* is defined in part as:

> Information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the [Agency] about, among other things, a serious risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was approved, or since the last assessment of the approved REMS.[8]

On September 10, 2013, FDA notified application holders for ER/LA opioid analgesics that, pursuant to section 505(o)(4) of the FD&C Act, safety labeling changes were needed for ER/LA opioid analgesics.[9,10] FDA explained its rationale, and the new safety information upon which it relied in exercising this authority.[11] The Agency intended these changes to more effectively communicate the serious risks of misuse, abuse, NOWS, addiction, overdose, and death associated with the use of ER/LA opioid analgesics.

The NOWS-related changes were based on new safety information derived primarily from a cross-sectional study by Stephen W. Patrick published in 2012 in the *Journal of the American*

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[4] *See* Finnegan LP, Connaughton JF, Jr., Kron RE, *et al.*, Neonatal abstinence syndrome: assessment and management. *Addictive diseases* 1975; 2:141-158.

[5] *See* Jansson L and Valez M. Neonatal abstinence syndrome. *Curr Opin Pediatr* 2012; 24:252-258.

[6] *Id.*

[7] 21 U.S.C 355(o)(4). *See also* Guidance for Industry: *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013) ("SLC Guidance").

[8] *See* section 505-1(b)(3) of the FD&C Act.

[9] Pursuant to section 505(o)(4) of the FD&C Act, FDA notified holders of approved NDAs and holders of approved ANDAs without a currently marketed reference listed drug approved under a NDA.

[10] *See* Letter to Application Holders: Labeling Supplement and PMR Required (SLC/PMR Letter), available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf.

[11] *See* SLC/PMR Letter at 1-2, describing certain safety labeling changes and post-marketing requirements (PMRs).

Medical Association (JAMA) (the "Patrick study").[12] As the Agency explained on page 2 of the SLC/PMR Letter:

> FDA has also become aware of the increasing frequency of neonatal abstinence syndrome (NAS), a term which includes [NOWS], as well as neonatal withdrawal from other drugs. An assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001).[13] The same study documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001]).[14]

The Agency determined that the above analysis, when taken together with other information and analyses, constituted new safety information about NOWS that should be included in the labeling for all ER/LA opioid analgesics.

The NOWS labeling set forth in the SLC/PMR Letter raised the prominence of the NOWS warning and better emphasized the need for providers to be prepared for NOWS. On April 7, 2014, FDA concluded the discussion period with the ER/LA opioid analgesic sponsors and approved NOWS labeling changes.[15] The final labeling is identical to the NOWS labeling set forth in the SLC/PMR Letter, except for the following changes (deletions in strikethrough and additions in bold). The changes clarify, among other things, that NOWS is potentially life-threatening **if not recognized and treated**:

- In the boxed warning in Highlights: "~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged use **of TRADENAME** during pregnancy can result in ~~life-threatening~~ neonatal opioid withdrawal syndrome**, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.X~~3~~).**"
- In the boxed warning: "Neonatal Opioid Withdrawal Syndrome: ~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged ~~maternal~~ use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening **if not recognized and treated,** and requires management according to protocols developed by neonatology experts**. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available** *[see Warnings and Precautions (5.X~~3~~)]*."

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[12] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307(18):1934-30.

[13] *Id.*

[14] *Id.*

[15] *See* 505(o)(4)(D) and SLC Guidance at 9.

- In the Warnings and Precautions section: "5.~~X3~~ Neonatal Opioid Withdrawal Syndrome: ~~For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome.~~ Prolonged ~~maternal~~ use of TRADENAME during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening **if not recognized and treated,** and requires management according to protocols developed by neonatology experts. **If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.**

  Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn."

- In section 8, Special Populations: "8.1 Pregnancy: **Clinical Considerations: Fetal/neonatal adverse reactions:** Prolonged use of opioid analgesics during pregnancy ~~may cause~~ **for medical or nonmedical purposes can result in physical dependence in the neonate and** neonatal opioid withdrawal syndrome **shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly** *[see Warnings and Precautions (5.~~X3~~)]*."

- In section 17, Patient Counseling Information: "Neonatal Opioid Withdrawal Syndrome: Inform female patients of reproductive potential that ~~chronic~~ **prolonged** use of TRADENAME during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening **if not recognized and treated** *[see Warnings and Precautions (5.~~X3~~)]*."

- In the Medication Guide, "Tell your healthcare provider if you are: pregnant or planning to become pregnant. ~~TRADENAME may harm your unborn baby. Long-term (chronic)~~ **Prolonged** use **of TRADENAME** during pregnancy can cause ~~life-threatening~~ withdrawal symptoms in your newborn baby **that could be life-threatening if not recognized and treated**."

II. DISCUSSION

The Petitions request that FDA stay the implementation of (*i.e.*, decline to implement) the NOWS labeling set forth in the SLC/PMR Letter. The Petitions also request that FDA eliminate, or stay implementation of, any references to NOWS as "life-threatening" in ER/LA opioid analgesic labeling. In addition, the Petitions request that FDA include several statements related to OST in the ER/LA opioid analgesic labeling, and that FDA provide its NOWS-related scientific assessments to an advisory committee for review. For the reasons described below, these requests are denied.

A. NOWS is Life-threatening if Not Recognized and Treated

The Petitions assert that NOWS is not life-threatening, and that the NOWS labeling described in the SLC/PMR letter is medically inaccurate and inconsistent with expert guidelines (Citizen Petition at 3-6 and 10-11; Petition for Stay at 2-5 and 9-11).[16] Specifically, the Petitions assert that "[t]here is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality," and that "NOWS, when it occurs, is diagnosable, treatable, and has not been associated with long-term adverse consequences (Citizen Petition at 4; Petition for Stay at 3). The Petitions request that FDA substitute the following language in Section 5.3 of the warnings and precautions section:

> Infants born to mothers exposed to opioids during pregnancy, for medical or nonmedical purposes, may develop an abstinence syndrome shortly after birth. This syndrome, which can present as irritability, hyperactivity and abnormal sleep patterns, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight, generally is readily recognized and treated, and is not associated with adverse long-term outcomes. (Petition at 2).

FDA agrees that NOWS is diagnosable and treatable. However, NOWS can be life-threatening if it goes unrecognized and therefore untreated.[17] If a mother has not been identified as an opioid user, the infant may not be monitored for the emergence of withdrawal symptoms. Similarly, if the mother requires use of an opioid for an extended period during pregnancy, but this has not been taken into consideration for impact on the newborn, the infant may not be monitored for the emergence of withdrawal symptoms. If an infant develops NOWS and doctors do not recognize it, or are not anticipating it, there could be problems with diagnosis or a delay in therapy. Failure to treat NOWS, in turn, could result in unnecessary distress in, and even threaten the lives of, infants who were exposed to opioids in utero. The American Academy of Pediatrics, in its clinical report on neonatal drug withdrawal, states that "withdrawal from opioids or sedative-hypnotic drugs may be life-threatening."[18] Other recent studies reflect the same view. For example, Jones, *et al.*, describe the characteristics of neonatal abstinence syndrome (NAS) — a term that includes withdrawal from opioids — by saying, "When left untreated NAS can result in serious illness (*e.g.* diarrhea, feeding difficulties, weight loss and seizures) and death."[19]

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[16] FDA also received comments to both dockets expressing concern regarding the characterization of NOWS as "life-threatening." *See* FDA-2012-P-1288-0004, FDA-2012-P-1289-0004 (both from the American College of Obstetricians and Gynecologists, attaching the American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012, and asserting that NOWS is "without subsequent pathophysiology").

[17] NOWS has been described as potentially "life-threatening" in some ER/LA opioid labeling since at least 2012. *See, e.g.*, Avinza (morphine sulfate) extended-release capsules Labeling, NDA 021260, approved 7/9/12 (Section 8.6: Neonatal Opioid Withdrawal Syndrome: ". . . Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and should be treated according to protocols developed by neonatology experts."), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021260s015lbl.pdf.

[18] American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560. This study does, however, acknowledge that "ultimately, drug withdrawal is a self-limited process."

[19] Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31. In support of this assertion, the authors cite a chapter by LP Finnegan in the second edition of Primary Pediatric Care, edited by RA Hoekelman, SE Friedman, NM Nelson, *et al.* *See id.*

The NOWS labeling changes approved on April 14, 2014 explicitly state that NOWS is potentially life-threatening **if not recognized and treated**. The Agency believes that these clarifying changes more precisely articulate the risks of NOWS. FDA also included this clarifying language to avoid any implication that ER/LA opioid analgesics should never be used during pregnancy due to the risk of NOWS. The Agency agrees that opioid therapy may be necessary for the health and well-being of a pregnant woman. It does not intend to discourage the medically appropriate use of opioids in pregnant women. [20]

FDA disagrees with the Petitions' assertions (and proposed labeling statement) that NOWS "is not associated with adverse long-term outcomes." Although data regarding long-term risks of NOWS are limited, and more research is needed, there are suggestions in published literature that NOWS may be associated with substantive long-term effects on neurologic and cognitive functioning.[21] Thus, at present, FDA has not determined that NOWS "is not associated with adverse long-term outcomes." [22]

B. Legal and Regulatory Requirements

1. Section 505(o)(4) of the FD&C Act

Pursuant to section 505(o)(4)(A) of the FD&C Act, "[i]f the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person." The Petitions and a comment to both dockets[23] challenge both the notion of NOWS as a "serious risk," and the propriety of FDA's reliance on a study by Patrick, *et al.*,[24] as the source of "new safety information . . . about a serious risk"[25] that forms the basis for the NOWS-related labeling changes. For the reasons described below, FDA disagrees.

A "serious risk" is a "risk of a serious adverse drug experience,"[26] which is defined as an adverse drug experience that:

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[20] For example, the boxed warning, and warnings and precautions sections state, "**If opioid use is required** for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available" (emphasis added).

[21] *See, e.g.*, Rosen TS and Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age *The Journal of Pediatrics* 1982; 101(2):192-196; Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders *Toxicology Letters* 2003; 140-141:171-181; Wahlsten VS and Sarman I. Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatrica* May 2013; 102(5):544-9.

[22] The Agency also notes that a risk does not need to be associated with "long-term" consequences to be included in drug labeling.

[23] FDA-2013-P-1288-0006, FDA-2012-P-1289-0005 (same comment).

[24] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307 (18): 1934-30.

[25] Section 505-1(b)(3)(A) of the FD&C Act (defining *new safety information*).

[26] Section 505-1(b)(5) of the FD&C Act.

(A) Results in:
1. Death;
2. An adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. A congenital anomaly or birth defect; or

(B) Based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).[27]

As stated above, NOWS may result in, among other things, diarrhea, feeding difficulties, weight loss, and seizures.[28] It thus can result in a prolongation of existing hospitalization, particularly in infants with severe symptoms who need opioid therapy.[29] Moreover, NOWS may require a medical intervention (*e.g.*, opioid treatment) to prevent inpatient hospitalization or prolongation of existing hospitalization.[30] NOWS therefore constitutes a "serious" risk as defined by statute, and thus is a valid subject for safety labeling changes under section 505(o)(4).[31]

Further, information derived from the Patrick study suggests an increasing incidence of NOWS,[32] and that the labeling of ER/LA opioids should emphasize NOWS risks and adding additional NOWS warnings. In particular, the Patrick study showed an increasing prevalence of opioid use during pregnancy and a concomitant increase in the rate of cases of NAS, including cases of NAS from opioids (*i.e.*, NOWS).[33] (The Patrick study also found that infants with NAS were significantly more likely to have respiratory diagnoses (30.9% of newborns with NAS vs.

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[27] Section 505-1(b)(4) of the FD&C Act.

[28] *See, e.g.*, Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010; 363:2320-31.

[29] *See* American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. *Pediatrics* 2012; 129:e540-e560.

[30] *See id.*

[31] Notably, although the "Warnings and Precautions" section requires the inclusion of "clinically significant" adverse reactions, such adverse reactions do not need to rise to the level of being "serious" to be included in the labeling. *See* 21 CFR 201.57(c)(6).

[32] Additional studies, though not relied upon as new safety information, also support this conclusion. *See* Creanga, AA, Sabel, JC, Ko, JY, Wasserman, CR, Shapiro-Mendoza, CK, Taylor, P, *et al.* (2012). Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstetrics and gynecology,* 119; 924-933; Kelly, L, Dooley, J, Cromarty, H, Minty, B, Morgan, A, Madden, S, *et al.* (2011). Narcotic-exposed neonates in a First Nations population in northwestern Ontario: incidence and implications. *Canadian family physician Medecin de famille canadien,* 57; e441-e447; Kellogg, A, Rose, CH, Harms, RH, & Watson, WJ (2011). Current trends in narcotic use in pregnancy and neonatal outcomes. *American journal of obstetrics and gynecology,* 204; 259-4.

[33] *See* n. 11 and 12, *supra.* Specifically, FDA found that this "assessment of a nationally representative Agency for Healthcare Research and Quality database showed that between 2000 and 2009, the rate of newborns diagnosed with NAS increased from 1.20 (95% CI, 1.04-1.37) to 3.39 (95% CI, 3.12-3.67) per 1000 hospital births per year (P for trend < .001). [The Patrick study also] documented a concurrent increase in the frequency of delivering mothers being diagnosed as dependent on or using opiates at the time of delivery (1.19 [95% CI, 1.01-1.35] to 5.63 [95% CI, 4.40-6.71] per 1000 hospital births per year [P for trend < .001])." SLC/PMR Letter at 3.

8.9% without NAS), feeding difficulty (18.1% vs. 2.8%), and seizures (2.3% vs. 0.1%).[34]) The Patrick study has certain limitations.[35] Nevertheless, although the study's limitations prevent establishment of a direct relationship between opioid use and opioid-related NAS, the increases over time in both NAS and opioid use during pregnancy are clear. The Agency thus decided to raise the prominence of these warnings so that physicians and patients are better able to use the drugs safely — both for mothers, who may need opioid therapy during pregnancy, and for infants, who may need prompt recognition of and treatment for NOWS.

2. Other Statutory and Regulatory Requirements

The Petitions also assert that the NOWS-related labeling included in the SLC/PMR Letter – and, thus, presumably, the labeling that FDA approved on April 14, 2014 – is false and misleading, and is not based on "a fair evaluation of all material facts" (Citizen Petition at 3, 6-7; Petition for Stay at 2, 5-7).[36] For example, the Petitions allege that the labeling violates 21 CFR 201.56(a)(2) (requiring labeling to be "informative and accurate" and not false or misleading) and (a)(3) (stating that "labeling must be based whenever possible on data derived from human experience," and that "[n]o implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness") on the grounds that there "is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality" (Citizen Petition at 4). FDA disagrees with these assertions.

FDA has considered the new safety information discussed in the SLC/PMR Letter, other relevant publications, as well as the information supplied in the Petitions, and has concluded that the NOWS labeling approved on April 14, 2014 complies with applicable statutory and regulatory requirements. First, both the publications describing NOWS as "life-threatening"[37] and the Patrick study involve data derived from human experience. Second, the labeling language Petitioner contests ("[p]rolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome") is neither false nor misleading. In particular, the Agency has determined that NOWS can be life-threatening, and believes that the finalized labeling language is both informative, accurate, and not misleading — particularly when one reads all NOWS

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[34] Patrick SW, Schumacher RE, Benneyworth BD, *et al.* Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009. *JAMA* 2012; 307 (18): 1934-30.

[35] Specifically, although the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes used in the analysis of maternal opiate exposures were specific to opioids, the ICD-9-CM code (779.5) used in the analysis of NAS was not specific to opioids. In addition, the data sources for NAS rate calculation and opioid use during pregnancy were unlinked. Petitioner also challenges the data from the Patrick study as, among other things, failing to distinguish between use of opioids as prescribed versus abuse or misuse and failing to reference the length of fetal opioid exposure. However, these concerns do not alter the Agency's continued reliance on the Patrick study in support of its NOWS labeling changes.

[36] The Petition contends that the NOWS-related labeling is not supported by "substantial evidence" as required by section 505(d)(5). However, substantial evidence is the standard for inclusion of information about effectiveness in the labeling. *See* FDCA 505(d)(5); 21 CFR 201.56(a)(3); Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998).

[37] *See, e.g.*, American Academy of Pediatrics Clinical Report Neonatal Drug Withdrawal. Pediatrics 2012; 129:e540-e560; Jones HE, Kaltenbach K, Heil SH, *et al.* Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 2010;363:2320-31.

sections of the new labeling, three of which state, "If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available."[38] This statement reflects FDA's recognition that ER/LA opioid analgesics may be necessary for some patients during pregnancy.[39] In addition, the ER/LA opioid analgesics' labeling as approved clarifies the risks NOWS presents, as it now includes the language: "[p]rolonged use during pregnancy can result in neonatal opioid withdrawal syndrome, which can be life-threatening **if not recognized and treated**" (emphasis added). This language emphasizes the importance of recognizing and treating NOWS as a part of neonatal care.

For the foregoing reasons, the language regarding NOWS in the labeling for ER/LA opioid analgesics complies with applicable statutory and regulatory requirements.[40]

C. Impact on Maternal and Fetal Health

Although the April 14, 2014 SLCs apply to ER/LA opioid analgesics, the Petitions' primary concern seems to be that the NOWS labeling may discourage opioid-addicted pregnant women from seeking or receiving addiction treatment, including OST. The Petitions also assert that the NOWS labeling "is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST" (Citizen Petition at 3, 11-15; Petition for Stay at 2, 11-15). The Citizen Petition thus requests several changes in the ER/LA opioid analgesics' labeling pertaining to both OST and NOWS.

FDA acknowledges the challenges faced by opioid-addicted pregnant women,[41] and agrees that OST can be an important component of their care. OST may also be important to fetal health, since abrupt opioid withdrawal during pregnancy can lead to fetal loss. FDA is not challenging the national and international guidelines[42] for care of opioid-addicted pregnant women, or the appropriate medical use of OST for these women during pregnancy. However, for the reasons discussed below, FDA declines to require the requested language as part of ER/LA opioid analgesics' labeling.

The Citizen Petition requests that FDA include the following language regarding OST in the ER/LA opioid analgesics' labeling (Petition at 2):

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[38] *See* the boxed warning in Highlights, the boxed warning, and section 5.3 of Warnings and Precautions.

[39] Notably, these drugs also are **not** contraindicated during pregnancy.

[40] *See* sections 505(d) and 505(o)(4) of the FD&C Act; 21 CFR 201.56, 57.

[41] Comments to the docket also have raised these concerns. *See, e.g.*, FDA-2013-P-1288-0005 (comment to the Citizen Petition docket).

[42] *See* American College of Obstetricians and Gynecologists Committee Opinion Opioid Abuse, Dependence, and Addiction in Pregnancy. Number 524, May 2012; Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction during pregnancy. Treatment improvement protocol series 43. Substance Abuse and Mental Health Services Administration; 2005, revised 2012, available at: http://www.ncbi.nlm.nih.gov/books/NBK26113; World Health Organization, Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence (2009). There are no national or international guidelines for opioid analgesia therapy during pregnancy, except for analgesia during labor. *See* American College of Obstetricians and Gynecologists Committee Opinion Obstetric analgesia and anesthesia. Number 36; July 2002.

- (1) Opioid dependence is a chronic, relapsing medical condition with high morbidity and significant risk of death. Opioid substitution treatment (OST) with methadone or buprenorphine is the best-proven way to reduce the harms of drug use for the individual and the community, including overdose, death and HIV infection. Persons found to be using [Tradename] without proper medical supervision or in a manner inconsistent with the prescribed dosage and/or duration should be encouraged to seek appropriate evaluation and treatment and offered assistance in doing so.

- (4) Opioid dependent pregnant women should be particularly encouraged to enter treatment since OST can lessen the risk of fetal demise and dramatically improve neonatal outcome. Physicians should be aware that infants born to mothers exposed to opioids during pregnancy for either medical or nonmedical purposes may be physically dependent on opioids and may develop an abstinence syndrome shortly after birth. Generally, this syndrome is readily recognized and treated, and is not associated with adverse long-term outcomes.

The suggested language in the first bullet (*i.e.*, suggested labeling paragraph (1)) above overstates the benefits of OST and fails to mention the risks of such treatment. Although FDA agrees that OST is an important method for managing opioid addiction, it is but one type of treatment. Nor is OST, in the absence of additional therapies, sufficient for all patients. Stating that "Opioid substitution treatment (OST) with methadone or buprenorphine is the best-proven way to reduce the harms of drug use..." would be an oversimplification of the management of opioid addiction.

In addition, FDA-approved labeling often alerts prescribers to risks associated with a drug without describing how to manage those risks. The labeling for ER/LA opioid analgesics, for example, informs prescribers about the risk of chronic pulmonary disease exacerbation, hypotension, raised intracranial pressure, worsened biliary tract disease, or aggravated seizures, but does not provide information about the treatment of these risks. FDA believes the approved labeling for the ER/LA opioid analgesics provides the essential scientific information that prescribers need in order to understand these risks, and the importance of identifying patients at risk and patients who begin to exhibit behaviors that may be associated with them.

The second suggested bullet (*i.e.*, suggested labeling paragraph (4)) above also overstates the benefits of OST, although for treatment of a labeled risk (addiction) in a specific population: pregnant women. Although FDA does not dispute the important role that OST may play in the care of opioid-addicted pregnant women, the Agency believes (as noted above) that the current labeling provides the essential scientific information for the safe use of these ER/LA opioid analgesics.

Suggested paragraph (4) also warns that babies born to opioid-dependent mothers may develop an abstinence syndrome – information that is already addressed in several places in the approved NOWS labeling – and a statement that NOWS is "readily recognized and treated, and is not associated with adverse long-term outcomes." However, based on a review of relevant published literature, FDA does not agree at this time that NOWS is not associated with long-term adverse consequences. Although available data regarding long-term risks of NOWS are limited, and more research should be done to evaluate the issue, there are suggestions in published literature that NOWS may be associated with substantive long-term effects on neurologic and cognitive

functioning.[43] Thus, at present, FDA is unable to conclude that NOWS "is not associated with adverse long-term outcomes."[44]

The Petition further requests that FDA replace section 5.3 of the Warnings and Precautions section of ER/LA opioid analgesic labeling with the following language:

- Infants born to mothers exposed to opioids during pregnancy, for medical or nonmedical purposes, may develop an abstinence syndrome shortly after birth. This syndrome, which can present as irritability, hyperactivity and abnormal sleep patterns, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight, generally is readily recognized and treated, and is not associated with adverse long-term outcomes.

- Opioid dependent pregnant women should be particularly encouraged to enter OST since this can lessen the risk of fetal demise and dramatically improve neonatal outcome.

(Petition at 2). Significantly, the NOWS labeling requested in the SLC/PMR Letter and approved on April 14, 2014 contains much of the language suggested in bullet 1, above. The exceptions are the statement that NOWS is "generally is readily recognized and treated, and is not associated with adverse long-term outcomes," and the language encouraging opioid-dependent pregnant women to use OST. This language is also suggested in the paragraph (4) labeling, FDA's response to which is discussed above.

For the foregoing reasons, FDA declines to require the requested language as part of ER/LA opioid analgesic labeling.

D. Request for Advisory Committee Review

Finally, the Citizen Petition requests that FDA present NOWS-specific literature reviews "justifying the labeling changes to an advisory committee so that the American public can be assured that any changes made to labeling will be evidence-based" (Citizen Petition at 3). FDA routinely assesses scientific literature and makes determinations regarding drug labeling, including pursuant to its SLC authority. Referring a matter to an advisory committee requires a substantial expenditure of resources and time, and the agency must prioritize these finite resources to the matters in which the agency would most benefit from the advice of outside

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[43] *See, e.g.*, Rosen TS and Johnson HL. Children of methadone-maintained mothers: follow-up to 18 months of age *The Journal of Pediatrics* 1982; 101(2):192-196; Ornoy A. The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: long-term neurobehavioral studies in children at risk for developmental disorders *Toxicology Letters* 2003; 140-141:171-181; Wahlsten VS and Sarman I. Neurobehavioral development of preschool age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatrica* May 2013; 102(5):544-9.

[44] Again, the Agency notes that a risk does not need to have "long-term" consequences to be included in drug labeling.

experts.[45] FDA therefore declines to convene an advisory committee meeting regarding NOWS labeling at this time.

III. CONCLUSION

For the foregoing reasons, and as described above, the Petitions are denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[45] *See* Draft Guidance for Industry: *Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings* at 4 (Aug. 2008). For example, FDA is likely to convene an advisory committee for a matter of "such significant public interest" or "so controversial" that advisory committee review is warranted, or if an advisory committee has a specialized expertise necessary for the agency's consideration.