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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION¹

National Advocates for Pregnant Women (NAPW), a 501(c)(3) non-profit advocacy and education organization that seeks to protect the rights and human dignity of all women, particularly pregnant and parenting women, respectfully submits this Citizen Petition to the Food and Drug Administration (FDA) under 21 C.F.R. § 10.30. In conjunction with medical and psychological researchers; treatment providers; reproductive health, drug policy, harm reduction, and criminal justice organizations throughout the country, NAPW requests that the Commissioner of Food and Drugs (1) refrain from implementing the FDA's neonatal opioid withdrawal syndrome (NOWS)-related labeling changes for extended-release and long-acting (ER/LA) opioid analgesics as announced on September 10, 2013, (2) present medical and scientific findings to an advisory committee to evaluate whether the proposed changes are justified, and (3) include specific language about the value of treatment for pregnant women who are opioid-dependent.

A. ACTION REQUESTED

This Citizen Petition respectfully requests that the Commissioner do the following:

- 1) Refrain from implementing the following FDA NOWS-related labeling changes for ER/LA opioid analgesics:
 - Boxed Warning: "For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome."
 - Full Prescribing Information: "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 and requires management according to protocols developed by neonatology experts."

¹ Please note that this Citizen Petition was filed concurrently with a Petition for Stay of Action pursuant to 21 C.F.R. § 10.35.

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- Warnings and Precautions (5.3): “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 and requires management according to protocols developed by neonatology experts.”
 - Patient Counseling Information: “Inform female patients of reproductive potential that chronic use of Tradename during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening.”
 - Medication Guide: “Tell your healthcare provider if you are pregnant or planning to become pregnant. Tradename may harm your unborn baby. Long-term (chronic) use during pregnancy can cause life-threatening withdrawal symptoms in your newborn baby.”
 - Any and all language not previously mentioned that refers to neonatal opioid withdrawal syndrome as life-threatening.
- 2) Remove the NOWS boxed warning.
 - 3) Remove all references to NOWS as life-threatening, including in the patient counseling information and medication guide.
 - 4) Modify the full prescribing information as follows to ensure that physicians who prescribe ER/LA opioid analgesics are appropriately informed about the nature and treatment of opioid dependence:
 - *(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.*
 - 5) Replace Section 5.3 of the warnings and precautions with the following:
 - *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.*
- 6) Require the FDA to present its issue-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.

B. STATEMENT OF GROUNDS

Petitioners do not dispute that the FDA has the authority to request safety labeling changes under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355. Neither do Petitioners dispute the potentially serious consequences of nonmedical use, misuse, or abuse of opioids, including opioid analgesics, nor the FDA's conclusion that serious outcomes are more likely to be associated with ER/LA opioid analgesics than with immediate-release opioids.

This Citizen Petition, however, challenges the FDA's Nows-related safety labeling changes as unsupported by medical and scientific evidence. The labeling changes are false and misleading and will likely result in pregnant women being denied adequate pain treatment, discourage opioid-dependent pregnant women from seeking and being offered potentially life-saving treatment, and increase the number of pregnant women who are charged with child abuse if they do receive this treatment. Petitioners' primary concerns are the following:

- 1) The Nows-related warnings are medically inaccurate and do not adhere to FDA labeling requirements.
- 2) FDA regulations required refusal of the Nows-related labeling changes because the new safety information did not present a serious risk, nor were the changes based on substantial evidence or a fair evaluation of all material facts.
- 3) The Nows-related warnings are inconsistent with leading national and international expert opinion on opioid use during pregnancy and other FDA regulations, and fail to consider the negative medical consequences of this labeling for maternal and fetal health.
- 4) The FDA's conclusion that Nows is life-threatening is erroneous.
- 5) This labeling is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST.

Each of these issues is more fully addressed below.

1) The Nows-related warnings are medically inaccurate and do not adhere to FDA labeling requirements.

The Code of Federal Regulations clearly lays out the FDA's labeling requirements for prescription drugs. 21 C.F.R. § 201 (2013). In addition to summarizing the essential scientific information that outlines the safe and effective use of the drug, the labeling must also be "informative and accurate and neither promotional in tone nor false or misleading in any particular." 21 C.F.R. § 201.56(a)(2). Moreover, "[t]he labeling must be based whenever possible on data derived from human experience. No 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.” 21 C.F.R. § 201.56(a)(3).

The NOWS-related warnings stating that “[p]rolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome” are both false and misleading. Such labeling, however, could very literally be life-threatening to pregnant women and the fertilized eggs, embryos, and fetuses they carry, nurture, and sustain. There is no rational connection between scientific and medical research on NOWS and statements regarding its potential lethality. In fact, Petitioners are not aware of a single reported case of fetal demise attributed to NOWS that has been diagnosed and treated according to the well-established protocols that have been employed for decades. NOWS, when it occurs, is diagnosable, treatable, and has not been associated with long-term adverse consequences.²

Petitioners do not deny that NOWS is often a consequence of *in utero* exposure to opioids, including opioids prescribed for pain management and OST. Indeed, Petitioners do not endorse materials that dismiss or minimize the possibility of NOWS.³ Nevertheless, it must also be noted that both the occurrence and severity of NOWS have been shown to be affected by a variety of factors that are unrelated to possible pharmacological effects of prenatal exposure to opiates. For example, one study demonstrated that when hospitals employed rooming in—the practice of caring for mother and newborn together in the same room immediately from birth—rather than placing them in neonatal intensive care units (NICU), newborns had less need for treatment of neonatal abstinence syndrome (NAS), shorter length of hospital stay, and significantly greater likelihood of being discharged home in the custody of their mothers.⁴ Similarly, a 2010 peer-reviewed study found that only 11% of babies who boarded with their mothers required treatment of NAS compared to more than four times as many who were placed in a NICU.⁵ In

² See Walter K. Kraft & John N. van den Anker, *Pharmacological Management of the Opioid Neonatal Abstinence Syndrome*, 59;5 *Pediatric Clinics of North America* 1147 (2012) (concluding that “there is no evidence of long term adverse outcomes in children treated with pharmacological agents vs. infants who do not require treatment for NAS . . .”); Stacy Seikel, *Methadone Treatment in Pregnancy . . . That Can't Be Right, Can It?*, 63;1 *N.E. Fla. Med.* 28, 29 (2012) (stating that research shows “minimal to no long-term negative sequelae on babies born to mothers who are on stable doses of methadone, engaged in psychosocial services, and in a stable living environment.”).

³ A 2012 pamphlet distributed by Reckitt Benckiser, manufacturer of Suboxone, misleadingly states that “[n]eonatal withdrawal *has been reported* following use of buprenorphine by the mother during pregnancy,” Suboxone Pamphlet (Jan., 2012), http://www.suboxone.com/hcp/resources/documents/SF_PhysLabeling_Brochure.pdf, when in fact, in one widely-publicized study, 47% of babies whose mothers received buprenorphine under highly controlled conditions not only were “reported” to have had NOWS, but received morphine to treat the condition. Hendrée E. Jones *et al.*, *Neonatal abstinence syndrome after methadone or buprenorphine exposure*, 363;24 *N. Eng. J. Med.* 2320 (2010).

⁴ Ronald R. Abrahams *et al.*, *An Evaluation of Rooming-In Among Substance-exposed Newborns in British Columbia*, 2010;32(9) *J. Obstet. Gynaecol. Can.* 866 (2010).

⁵ Tolulope Saiki *et al.*, 169 *Eur. J. Peds.* 95 (2010).

addition, allowing mothers to breastfeed their newborns can reduce the need for NICU and medications.⁶

Evidence-based research also shows that location was associated with major differences in the treatment of NOWS. For example, “. . . to babies whose mothers received methadone [during pregnancy,] the total morphine dose administered to control neonatal abstinence syndrome averaged 4.93 mg in rural American sites, 5.04 mg in Vienna, and 34.17 mg in urban U.S. sites; the number of days of medication averaged 4.92, 9.26 and 17.91, respectively.”⁷

NOWS can be evaluated and managed with scoring systems and treatment protocols that have been available for decades in standard textbooks and in numerous articles in the professional literature. Appropriate care, which may include breastfeeding and “comfort care” (e.g., swaddling and skin-to-skin contact between mother and baby), is often sufficient to prevent or minimize signs of distress in the baby. In the words of the Substance Abuse and Mental Health Services Administration (SAMHSA):

Many times a quiet, comfortable environment is enough to provide comfort to your baby. If the symptoms are severe, your baby’s doctor may prescribe medicine to help. . . . The good news is that babies born to mothers on methadone do as well as other babies; their health is much better than babies born to mothers on heroin.⁸

In spite of this research, the NOWS-related warnings draw no distinction between use and misuse of heroin or prescription opioids and opioids utilized by health care professionals in managing the pain management of pregnant women or the care of dependent pregnant women. The labeling includes numerous warnings about the consequences of NOWS, including—inaccurately—fetal demise, yet fails to provide patient counseling information explaining appropriate medical management. This is particularly problematic in a field where health care providers often lack even minimum training and where disorders associated with opiate use are highly stigmatized.⁹

⁶ Mohamed E. Abdel-Latif *et al.*, *Effects of Breast Milk on the Severity and Outcome of Neonatal Abstinence Syndrome Among Infants of Drug-Dependent Mothers*, 117;6 *Pediatrics* 1163 (2006).

⁷ Robert Newman & Susan Gevertz, *The Complex Factors Determining Neonatal Abstinence Syndrome and Its Management*, 18 *Eur. Addict. Res.* 322 (2012) (citing data in a publication by A. Baewert *et al.*, 18 *Eur. Addict. Res.* 130 (2012)).

⁸ Substance Abuse & Mental Health Services Administration, U.S. Dep’t of Health & Human Services, Pub. No. [SMA] 06-4124, *Methadone Treatment for Pregnant Women* (2006) *available at* <http://www.atforum.com/addiction-resources/documents/SAMHSAbrochurePregnantWomen2006.080904-39-5315-04-44.pdf>.

⁹ See National Center on Addiction and Substance Abuse at Columbia University, *Addiction Medicine: Closing the Gap Between Science and Practice* (2012) *available at* <http://www.casacolumbia.org/upload/2012/20120626addictionmed.pdf> (stating that physicians “lack the basic education and training in addiction medicine that is needed to understand the science of addiction [and] translate research evidence into practice”); White House Office of National Drug Control Policy, <http://www.whitehouse.gov/ondcp/drugpolicyreform> (last

Therefore, the NOWS-related labeling is false and misleading, does not comply with FDA labeling regulations, and should be changed to reflect medically accurate, informed, and sensitive treatment-focused options for pregnant women and the fertilized eggs, embryos, and fetuses they carry.

2) FDA regulations required refusal of the NOWS-related labeling changes because the new safety information did not present a serious risk, nor were the changes based on substantial evidence or a fair evaluation of all material facts.

In addition to the general labeling requirements defined in 21 C.F.R. § 201, Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act authorizes the FDA to require and, if necessary, order labeling changes if the FDA becomes aware of new safety information that it believes should be included in the labeling of a drug. 21 U.S.C. § 355(o)(4).

New safety information is defined as “information derived from clinical trial, an adverse event report, a postapproval study . . . , peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 355(k) of this title; or other scientific data deemed appropriate” 21. U.S.C. § 355–1(b)(3). Other scientific data may be presented as either:

(A) a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

21. U.S.C. § 355–1(b)(3)(A)–(B). The term serious risk means a risk of a “serious adverse drug experience,” including death or placing the patient at immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. 21. U.S.C. § 355–1(b)(4)(A). A serious adverse drug experience may also be one that, “based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described [above].” 355–1(b)(4)(B).

Here, however, Petitioners are not aware of a single reported case of fetal demise attributed to NOWS that has been diagnosed and treated according to the well-established protocols that have been employed for decades. To the contrary, leading national and international experts have overwhelmingly concluded that proper treatment for opioid dependency can be lifesaving for the

visited Oct. 1, 2013) (stating that “discussion of substance use disorders is too often relegated to the shadows, steeped in stigma and misunderstanding.”).

pregnant woman and her future child.¹⁰ A committee opinion by the American College of Obstetricians and Gynecologists (ACOG) states that “[n]eonatal abstinence syndrome is an expected and treatable condition that follows prenatal exposure to opioid agonists.”¹¹ Research also shows that it has not been associated with any long-term adverse consequences.¹² Accordingly, the NOWS-related safety labeling changes are inappropriate and misleading.

Alternatively, there are also seven grounds that *require* the refusal of an application or supplemental application, including relabeling, in 21 U.S.C. § 355(d)(2013). Petitioners focus on (5) and (7), but emphasize that any one of the seven grounds, on its own, would require refusal.

21 U.S.C. § 355(d)(5) explains that the refusal is required if, “. . . there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.” Substantial evidence is defined as:

. . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C. § 355(e). Here, there is not simply a lack of “substantial evidence” showing that NOWS is life-threatening; there is no evidence whatsoever. To reiterate: “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience” shows that NOWS is diagnosable and treatable, and has not been associated with any long-term adverse consequences.

Another ground that requires refusal is if, “based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.” 21 U.S.C. § 355(d)(7). Here, the NOWS boxed warning is indisputably false and misleading. Indeed, leading national and international experts have overwhelmingly concluded that proper treatment for opioid dependency can be lifesaving for the pregnant woman and her future child.

Therefore, even if the FDA had the ability to approve safety labeling changes under 21 U.S.C. 355(o)(4), the evidentiary threshold for doing so conflicts with the strict standards in 21 U.S.C. § 355(d). As they currently stand, FDA regulations for labeling and relabeling vary dramatically, and as such, the FDA should have issued an order refusing to approve the NOWS-related warnings of the relabeling application.

¹⁰ The American College of Obstetricians and Gynecologists, *Opioid Abuse, Dependence, and Addiction in Pregnancy*, Committee Opinion No. 524 (May 2012) available at <http://www.acog.org/~media/Committee%20Opinions/Committee%20on%20Health%20Care%20for%20Underserved%20Women/co524.pdf?dmc=1&ts=20130723T0355371185>.

¹¹ *Id.*

¹² See Kraft, Seikel, *supra* note 2.

3) The NOWS-related warnings are inconsistent with leading national and international expert opinion on opioid use during pregnancy and other FDA regulations, and fail to consider the negative consequences of this labeling for maternal and fetal health.

By inaccurately focusing on NOWS, the FDA's warnings fail to recognize that abrupt discontinuation and/or wide swings in concentration levels of opioids during pregnancy may cause fetal distress and pregnancy loss.¹³ Leading national and international experts urge pregnant women to seek treatment in lieu of stopping opioid intake altogether.

A SAMHSA brochure directed at opioid-dependent pregnant women states:

If you're pregnant and using drugs such as heroin or abusing opioid prescription pain killers, it's important that you get help for yourself and your unborn baby. Methadone maintenance treatment can help you stop using those drugs. It is safe for the baby, keeps you free of withdrawal, and gives you a chance to take care of yourself. . . . *MMT can save your baby's life.*¹⁴

Discontinuation of opiate substitution treatment during pregnancy is likely to result in relapse to nonmedical use of opioids, including IV heroin, which substantially increases risk to both the expectant mothers and their babies.¹⁵ The efficacy and safety of OST have been well documented in many countries over many years and OST is strongly endorsed by the World Health Organization, United Nations Office on Drugs and Crime, and the Joint United Nations Programme on HIV/AIDS. In March, 2013, a United Nations report condemned addiction treatment policies or lack thereof in some parts of the world as "tantamount to torture or cruel, inhuman or degrading treatment."¹⁶ The report stated that a "particular form of ill-treatment and possibly torture of drug users is the denial of opiate substitution treatment," and it is considered a human rights violation when it occurs in jails and prisons.¹⁷

¹³ The American College of Obstetricians and Gynecologists, *Nonmedical Use of Prescription Drugs*, Committee Opinion No. 538 (Oct. 2012) available at <http://www.acog.org/~media/Committee%20Opinions/Committee%20on%20Health%20Care%20for%20Underserved%20Women/co524.pdf?dmc=1&ts=20130723T0355371185>.

¹⁴ See SAMHSA *supra* note 8 (emphasis added).

¹⁵ World Health Organization, *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence* (2009) available at http://whqlibdoc.who.int/publications/2009/9789241547543_eng.pdf.

¹⁶ U.N. Human Rights Council, *Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment*, U.N. Doc. A/HRC/22/53 (Feb. 1, 2013) (by Juan E. Méndez) available at http://www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf.

¹⁷ *Id.*

The World Health Organization states:

For women who are pregnant or breastfeeding, opioid agonist maintenance with methadone is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on antenatal care and parenting of young children. Opioid-dependent women not in treatment should be encouraged to start opioid agonist maintenance treatment with methadone or buprenorphine. Pregnant women who are taking opioid agonist maintenance treatment should be encouraged not to cease it while they are pregnant. Although many women want to cease using opioids when they find out they are pregnant, opioid withdrawal is a high-risk option because a relapse to heroin use will affect the capacity to care for the child. In addition, severe opioid withdrawal symptoms may induce a spontaneous abortion in the first trimester of pregnancy, or premature labour in the third trimester.¹⁸

Medical research indisputably shows that the critical problem is not NOWS, but maternal dependence on opioids that goes untreated. As already stated throughout this Citizen Petition, proper treatment for opioid dependent pregnant women is not only appropriate, but also can be life-saving. Indeed, the FDA itself recognizes the special role that methadone can play in protecting the health and well-being of the opioid-dependent pregnant woman and her expectant child. For instance, the FDA's federal opioid treatment standards require that there be "... a preference for pregnant women in admitting patients to interim maintenance [when a position is not immediately available in a "comprehensive" OTP] and in transferring from interim maintenance to comprehensive maintenance treatment." 42 CFR § 8.12(j)(1). Another regulation carves out a "treatment admission exception" for pregnant patients. 42 CFR § 8.12(e)(3). Clearly, the FDA promulgated these regulations prioritizing treatment for pregnant women because it understands the grave risks associated with the abrupt discontinuation of opioids and their continued misuse or abuse, and the protective role that can be played by OST.

Moreover, even for women who are not opioid-dependent, "there are very few options for the treatment of severe chronic pain during pregnancy, and opioid analgesics have been relied upon as the safest alternative in conditions requiring treatment for pain."¹⁹ Obviously, pain does not disappear when a woman becomes pregnant, and women during pregnancy can and do experience pain from a variety of causes, but nevertheless, the NOWS-related warnings will likely result in pregnant women being denied adequate pain treatment.

This would not only be inhumane, but we also do not clearly know the impact of untreated pain during pregnancy. Untreated pain would certainly present a major stressor for the pregnant woman and her fetus, with potential adverse effects. This concern applies not only to pain throughout pregnancy but also pain during labor and delivery,

¹⁸ World Health Organization, *supra* note 11.

¹⁹ Letter from Massachusetts Society for Addiction Medicine to Martha Coakley, Massachusetts Attorney General, (June 6, 2013) *available at* http://masam.org/yahoo_site_admin/assets/docs/Coakley_letter_BlackBox_State_AG_FDA_response.156114529.pdf.

where judicious use of narcotic medications is often necessary, and for which safe administration protocols have been developed by obstetricians and anesthesiologists.²⁰

Unfortunately, the FDA's NOWS-related warnings, contrary to all relevant evidence, seem intended to discourage pregnant women from seeking appropriate pain treatment or appropriate and potentially life-saving treatment for dependence.

4) The FDA's conclusion that NOWS is life-threatening is erroneous.

In its letter to application holders for ER/LA opioid analgesics, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(o)(4)), the FDA states:

FDA has also become aware of the increasing frequency of neonatal abstinence syndrome (NAS), a term which includes neonatal opioid withdrawal syndrome (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). 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]). . . . FDA has determined that these study findings, in addition to the data and information discussed above, demonstrate the continuing trends of serious risks related to the use of opioid analgesics, and the need for modifications to product labeling to more effectively communicate the serious risks associated with ER/LA opioid analgesic use overall, and during pregnancy, and to more clearly describe the population in whom these drugs should be used, in light of these serious risks.²¹

Neither this paragraph, nor the sole study to which it refers, states that NOWS is life-threatening. The only reference cited did not even study morbidity or mortality of either mothers or their offspring, but rather, describes incidence during four separate years of NOWS and of "mothers diagnosed with antepartum opiate use."²² The study presented data from two obviously very different databases because during the years in question, data was analyzed for 9,674 babies with NAS, but for just 4,563 mothers with reported opiate use during pregnancy.²³ Furthermore, the study made absolutely no distinction between prescribed use and misuse or abuse of drugs, nor whether used illicitly or taken as prescribed for management of dependence or pain. Nor was there any reference to whether fetal exposure occurred over the course of days, weeks, or months

²⁰ *Id.*

²¹ Letter from FDA to ER/LA opioid analgesic application holders (Sept. 10, 2013) *available at* <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf>.

²² Stephen Patrick *et al.*, *Neonatal Abstinence Syndrome and Associated Health Care Expenditures: United States, 2000-2009* 307;18 JAMA 1934 (2012).

²³ *Id.*

prior to delivery. With respect to methadone in particular, data was lumped together with all other opiates, without regard to whether it was taken as part of a prescribed treatment regimen and, if so, whether given for management of pain or for dependence. By relying on this single study—one that does not even address fatality—the FDA has failed to acknowledge the extensive worldwide literature on the subject.

Petitioners are aware that there are reports claiming to identify major adverse effects, beyond merely the occurrence of NOWS, on the neonate as a result of *in utero* exposure to opioids. For example, a 2009 publication reported on a retrospective study of 450 babies whose mothers had received methadone treatment for opioid dependence during pregnancy.²⁴ The authors concluded that these infants “... are extremely vulnerable and draw heavily on healthcare resources.”²⁵ Like many others in this field, however, this study was flawed. It failed to consider that the amount of methadone being given to the pregnant women was significantly below recommended doses and neglected to take into account the duration of the treatment given. The “median daily prescribed dose of methadone” was 50 mg, which is well below what is recognized as being associated with optimal outcomes (60 – 100 mg per day for most patients, with higher doses generally required during pregnancy).²⁶ Also, the mothers could have been receiving OST throughout their pregnancy or for only a few days before delivery.²⁷

Another study in 2002 specifically analyzed the “relationship between maternal methadone [maintenance] dosage and neonatal withdrawal,” and concluded that “[m]aternal methadone dosage was associated [directly] with duration of neonatal hospitalization, neonatal abstinence score, and treatment for withdrawal.”²⁸ In this case, the median dose of methadone during gestation was 20 mg, which is substantially less than what is recognized as being associated with optimal outcomes.²⁹

Therefore, while Petitioners acknowledge that there is conflicting data on the prevalence of NOWS and some research suggesting some health consequences or influences following proper treatment, there still remains no study specifically claiming that NOWS is life-threatening.

5) This labeling is likely to increase erroneous and counterproductive child welfare actions against pregnant women and parents who receive OST.

The FDA’s relabeling will occur in a real life context in which health care providers and child welfare workers who are poorly trained in addiction treatment are likely to use the NOWS-related warnings to justify punitive and counterproductive child welfare interventions against pregnant women and new parents. This concern is not hypothetical. Today, even without the

²⁴ C. Dryden *et al.*, *Maternal methadone use and the consequences on baby*, 116 BJOG 665 (2009).

²⁵ *Id.*

²⁶ *Id.*

²⁷ *Id.*

²⁸ J.S. Dashe *et al.*, *Relationship between maternal methadone dosage and neonatal withdrawal*, 100 Obstet. Gynecol. 1244 (2002).

²⁹ *Id.*

false and misleading NOWS-related warnings challenged in this Citizen Petition, misinformation about and prejudice against OST have resulted in punitive child welfare actions taken against pregnant women and parents because they receive such treatment.

While this specific misuse of the child welfare system has not been subject to systematic study, and despite the fact that child welfare proceedings are generally confidential and do not come to public attention, NAPW has identified numerous cases in which state authorities have sought to punish pregnant women because they obtained medically approved methadone treatment. Over the past several years, NAPW has also received numerous requests for help from methadone treatment providers reporting punitive child welfare interventions.

For example, a staff member at a Michigan methadone maintenance facility wrote to NAPW seeking help because women participating in methadone maintenance treatment (MMT) were being placed on the abuse and neglect registry by local child protective services “for the sole reason of being on methadone maintenance during pregnancy.” The staff member explained:

Our local hospitals, court system, and Child Protective Services are opening cases on any woman whose child experiences neonatal abstinence syndrome after birth. The fact that the woman was legitimately participating in MMT and under a doctor's care is irrelevant to these agencies. . . . It is infuriating that none of these professionals are open to reviewing the facts about treatment and would instead criminalize women who have done nothing but make the right choice to participate in treatment for the sake of their child. CPS is also informing women that they are not allowed to breast feed while on methadone, unless they are tapering out of the program. If they continue to breast feed without tapering, they will be taken to court. The fact that all research and medical findings support breastfeeding while on methadone is being ignored. The uninformed actions of CPS are preventing women from seeking a potentially life saving treatment. We have heard of many women who have opted to continue illicit drug use rather than get the help that they need because of the actions of CPS. They are not telling their physician that they use drugs, and are discharged from the hospital before withdrawals set in. This means that babies are going through withdrawal at home, without needed medical attention. . . . I work with some amazing women who have made great strides in their recovery. The discrimination and harassment they are currently going through breaks my heart.³⁰

NAPW has received similar requests for help from methadone treatment providers in Tennessee and Georgia. The administrator of a new methadone treatment program in Georgia wrote: “I have 5 patients with varying degrees of problems with the DHR Division of Child and Family Services. Most of our patients are unable to hire private attorneys to fight for their children. The problem is one of ignorance, prejudice and misinformation about addiction as an illness and recovery as a process.”³¹ One of the examples provided:

³⁰ Email from P.S. to NAPW (May 22, 2012) (on file with NAPW).

³¹ Email from R.R. to NAPW (July 3, 2005) (on file with NAPW).

A new mother whose baby showed signs of withdrawal (which is typical, babies born to methadone patients may be physically dependent at birth and must be treated for withdrawal) in the hospital has lost custody to a foster family with “special training” to manage its treatment. This mother was compliant with treatment and not using illicit drugs. This case went in front of a juvenile judge.³²

In Tennessee, in just the past four months, two women contacted NAPW because judges overseeing child welfare cases demanded that mothers “detox from methadone” if they wanted to maintain or regain custody of their children. In both cases, the mothers were receiving therapeutic MMT as prescribed by their physicians.³³

In California, the Department of Children and Family Services removed newborn twins from their mother because she had received methadone treatment during pregnancy and the babies had displayed signs of NAS at birth. *In re C.R. v. R.H.*, 2012 WL 4049010, at *1 (Cal. Ct. App. 2d. Sept. 14, 2012). The juvenile court found that there was substantial evidence of a risk of harm to the children because “they suffered physical harm as a direct result of mother’s drug abuse issues.” *Id.* at *4. On appeal, the mother’s obstetrician testified on her behalf, explaining that:

[The twins] would not have experienced those symptoms if mother had been allowed to breast feed them as planned. The obstetrician also opined that mother’s methadone levels were appropriate, and that reducing or stopping methadone during pregnancy could have caused the twins to suffer withdrawal symptoms in utero serious enough to cause a loss of the pregnancy.

Id. at *3. Nevertheless, the appellate court upheld the juvenile court’s decision to separate the babies from their mother permanently.

In one of the many cases in which NAPW participated, a new mother in Connecticut who had been enrolled in methadone treatment while pregnant was charged with child abuse and neglect under the state’s civil child welfare law. *In re R.C.*, No. T11-CP04-011978-A (Conn. Super. Ct. 2005). This mother had received regular prenatal care, provided her physicians with complete and honest information regarding her medical history, and attempted to comply with all requests by both her methadone treatment program and the hospital staff after delivery. Staff at the hospital, however, were so inadequately trained and unfamiliar with methadone treatment that they viewed it as no different from active addiction and contacted the Department of Children and Families. The Department, in turn, drew on the same erroneous conclusion and charged the new mother with child abuse and neglect.

In another case discussed in a 2012 article, a family court judge told a mother that he would not close her child welfare case until she “got off methadone.”³⁴ When she introduced letters from

³² *Id.*

³³ Email from A.F. to NAPW (Aug. 8, 2013) (on file with NAPW); Email from R.N. to NAPW (Sept. 27, 2013) (on file with NAPW).

³⁴ Rachel Blustain, *Medical Consensus or Child Abuse? Moms on Methadone Caught in the Middle*, *The Daily Beast* (Sept. 2, 2012),

experts testifying that the federal government recommends methadone maintenance for opiate-addicted women, she said the judge ignored the medical evidence, telling her, "I can make an airplane out of these papers and glide it across the courtroom."³⁵

New Jersey provides a particularly clear example of state action taken against pregnant women who have received methadone treatment. For example, in *N.J. Div. of Youth & Family Servs. v. E.P.A.*, No. A-6169-05, slip op. at 13 (App. Div. Oct. 15, 2007), a mother was charged with parental neglect because her son tested positive for methadone at birth. The court received a letter from her treatment center confirming that she "had refrained from drug use, except methadone, for seventeen months," clarifying that she had not used any illegal drugs in the six months before she became pregnant and throughout her entire pregnancy. Nevertheless, the court characterized the receipt of prescribed methadone as "an inability to eliminate a reliance on methadone, itself an addictive drug," and upheld the lower court's order terminating the mother's parental rights.

A court in a similar case likened drug treatment to heroin use, finding neglect because "a woman using heroin or on methadone maintenance should find out about the risks to a child before becoming pregnant and opt to avoid that harm if the risks are great." *N.J. Div. of Youth & Family Servs. v. E.C.*, No. A-4219-06, slip op. at 12 (App. Div. Apr. 28, 2008) (emphasis added). The court found harm because the NAS the child allegedly experienced arose "[a]s a consequence of E.C.'s need for methadone, prescribed or otherwise." *Id.* at 19.

In *N.J. Div. of Youth & Family Servs. v. A.J.*, No. FN 07-346-10 (Law Div. Feb. 22, 2011), a woman who took prescribed methadone throughout her pregnancy as directed by her physician was reported for child abuse and neglect because the infant presented with NAS at birth. In the only case NAPW could find in which there was any evidence presented by scientific experts regarding addiction and methadone treatment during pregnancy, the trial court held that the Division of Child Protection and Permanency had failed to meet its burden to prove that a child was abused and neglected. This decision, which held that "the evidence supports a finding that his diagnosis, at birth, of Neonate Addiction Syndrome [sic] is an outcome that is consistent with the medical standard of care for opioid addicted pregnant women," was never published. Slip Op. at 32.

Most recently, however, a New Jersey appellate court in *N.J. Div. of Youth & Family Servs. v. Y.N.*, A-5880-11T2, 66 A.3d 237 (App. Div. 2013), upheld a lower court ruling that a newborn was abused and neglected because, after birth, he experienced NAS. The child's mother, while pregnant, obtained federally recommended, medically approved, and supervised methadone treatment from a methadone treatment program. She sought treatment to help her address an addiction to prescription Percocet, and her doctor advised her that abrupt withdrawal from Percocet could risk harm to the fetus, potentially causing her to lose the pregnancy altogether. Her treatment was successful and she was able to abstain from the use of illegal drugs during her pregnancy.

<http://www.thedailybeast.com/articles/2012/09/02/medical-consensus-or-child-abuse-moms-on-methadone-caught-in-the-middle.html>.

³⁵ *Id.*

The baby was born healthy, full term, with Apgar scores of 8 and 9.5. Shortly after birth, the baby showed the predicted signs of NAS, for which he was successfully treated, and was released from the NICU to his mother. In spite of this success story, the mother was reported to the Division of Youth and Family Services, which subsequently charged her with abuse and neglect. The trial court found that the child suffered harm due to a positive drug screen for methadone and a diagnosis of NAS. The New Jersey Court of Appeals upheld this ruling, concluding that the expected and treatable side effects of methadone treatment obtained by a pregnant woman may be treated as “harm” for purposes of the state’s abuse and neglect statute. N.J.S.A. 9:6-8.21(c)(4).

The effect of this ruling, if not overturned by the New Jersey Supreme Court, will be a judicially created penalty on pregnant women who obtain methadone treatment: obtain such treatment and lose your constitutional right to parent that child once born. The mother is currently seeking review by the state supreme court. She is supported by more than four dozen national and international experts and organizations in an amicus (friend of the court) brief.³⁶

NAPW has also identified or been contacted about numerous other cases in Alabama, Florida, Kentucky, Michigan, New York, Pennsylvania, South Carolina, and Texas, where pregnant women and parents have been threatened with loss of custody of their children or have actually lost custody of their children because they have been receiving some form of OST.

These cases have occurred even without the FDA’s labeling changes. The Nows-related warnings will undoubtedly increase the likelihood of such cases that endanger the health of pregnant women and new mothers by creating penalties for the receipt of OST.

In addition, failure of the FDA to draw any distinction between the use or misuse of opioids and compliance with a prescribed, strongly endorsed, evidence-based therapeutic regimen will also discourage women who need help from seeking it. This failure, not Nows, is what could truly prove life-threatening for pregnant women and their babies.

Conclusion

For the foregoing reasons, there is no rational connection between the available research on Nows and the FDA’s Nows-related warnings. The labeling changes are totally lacking in scientific support and the professional views of experts in the field. Indeed, the FDA’s decision is so implausible that it cannot be ascribed to a difference in view or the product of agency expertise. It will prove harmful to many pregnant women and their babies, and surely will result in the death of some. It will also severely impact the credibility of this agency, which plays such a crucial role in safeguarding the healthcare of the American public.

³⁶ Brief of *Amici Curaie* in Support of Defendant-Petitioner’s Petition for Certification, *N.J. Div. of Youth & Family Servs. v. Y.N.*, A-5880-11T2, 66 A.3d 237 (App. Div. 2013) (Aug. 1, 2013), available at http://www.advocatesforpregnantwomen.org/main/publications/brief_bank/.

C. ENVIRONMENTAL IMPACT

According to 21 C.F.R. 25.31, this Citizen Petition qualifies for a categorical exclusion from the requirement for the submission of an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of this Citizen Petition.

E. 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 includes representative data and information known to the Petitioners that are unfavorable to the Citizen Petition.

Respectfully submitted,

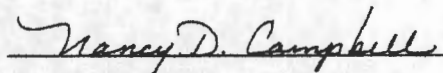
National Advocates for Pregnant Women
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American Association for the Treatment of
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Abortion Care Network (ACN)
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American College of Obstetricians and
Gynecologists (ACOG)
Washington, DC, USA

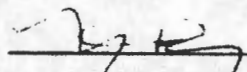
Drug Policy Alliance (DPA)
New York, NY, USA



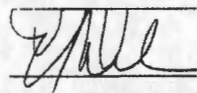
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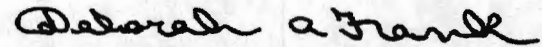
National Council on Alcoholism and Drug
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National Women's Health Network
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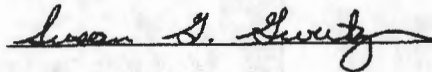
Project R.E.S.P.E.C.T. Substance Abuse
Disorder Treatment in Pregnancy Program
Boston, MA, USA



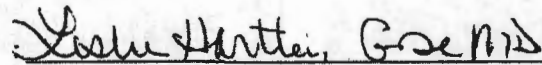
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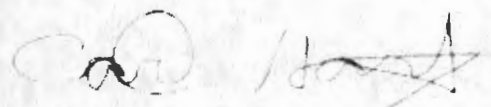
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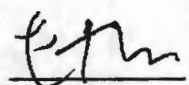
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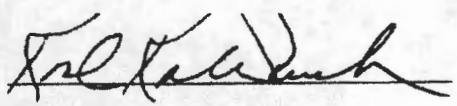
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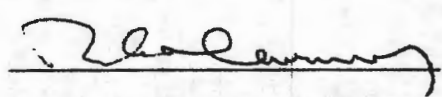
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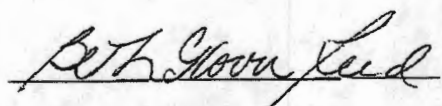


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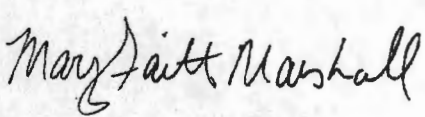


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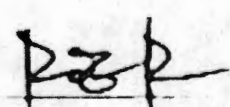
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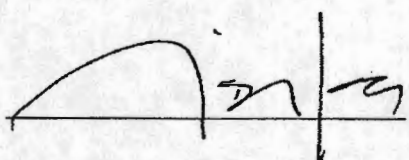
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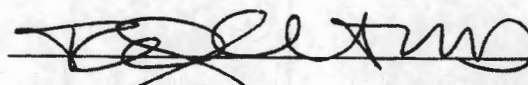
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