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July 8, 2016

The Honorable Sylvia M. Burwell
Secretary of Health and Human Services
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Secretary Burwell:

I write to inquire about the process by which the U.S. Department of Health and Human Services (HHS) tracks information on how biological and physiological characteristics specific to women can impact opioid sensitivity, prevalence of addiction, and the effectiveness of available treatments.

As of 2014, approximately 65,000 people in Massachusetts are dependent on opioids with almost 50,000 in need of treatment¹ for their addiction. More people die of opioid overdoses in the Commonwealth than are killed in motor vehicle crashes,² with 1,282 confirmed deaths in 2014³ compared to 328 vehicle occupant fatalities⁴ that same year. The opioid crisis is not just a New England issue, but a national epidemic. There was a 3.4-fold increase in the total number of U.S. deaths involving opioid pain relievers from 2001 to 2014.⁵

Gender and sex differences in opioid drug abuse may dictate whether certain characteristics are connected to addiction. Further understanding the variables that contribute to susceptibility may help focus treatments to mitigate future cases of opioid dependence. Even though the number of drug overdose deaths is greater among men, the percentage increase is higher among women.⁶ “Research has shown that women often use drugs differently, respond to drugs differently, and can have unique obstacles to effective treatment ... [such as] being prescribed treatment that has

¹ Data collected from SAMHSA’s National Survey on Drug Use and Health as analyzed by the Institute for Clinical and Economic Review Comparative Effectiveness Public Advisory Council.

² <http://www.mass.gov/eohhs/docs/dph/substance-abuse/opioid/overdoserresponsestrategies.pdf>

³ <http://www.mass.gov/eohhs/docs/dph/quality/drugcontrol/county-level-pmp/data-brief-overdose-deaths-may-2016.pdf>

⁴ <http://www.iihs.org/iihs/topics/t/general-statistics/fatalityfacts/state-by-state-overview>

⁵ <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>

⁶ <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6226a3.htm>

not been adequately tested on women.”⁷ One third of the patients battling opioid dependence are women of childbearing age,⁸ and women who use both prescription and illicit opioids during pregnancy may increase potential adverse outcomes such as congenital birth defects and neonatal abstinence syndrome.⁹ Additionally, opioids have historically been a commonly administered analgesia for postoperative pain management after a caesarean section.¹⁰ I am concerned that prescribed opioid use after birth can inadvertently lead to dependence for some mothers as they heal and adjust to life with their new infant.

The lack of knowledge about how different populations and subgroups respond to drugs led to the development of several federal initiatives. The National Institutes of Health (NIH) Revitalization Act of 1993 required NIH to develop guidelines for the inclusion of women and minorities in clinical research.¹¹ A month later, the U.S. Food and Drug Administration issued, “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs,” which, among other things, “called for analyzing trials by gender and for evaluating pharmacokinetics in women.”¹² In 1998, FDA published the ‘Demographic Rule’ which required sponsors to tabulate the numbers of participants in clinical trials by age group, gender, and race in investigational new drug application annual reports.¹³ A Government Accountability Office study about the progress of including women in research highlighted Institute of Medicine reports which emphasized that continued efforts by NIH – and others – are necessary, “to improve both the overall status of women’s health research and, in particular, the ability of researchers to conduct analysis of study results by sex to determine whether outcomes differ for women compared to men.”¹⁴

In order to better understand the progress HHS has made to study the impact of opioids on women, I ask that you respond to the following questions by August 1, 2016.

1. Have women been incorporated into NIH clinical research trials as required by the NIH Revitalization Act of 1993?
 - a. If so, have any clinical trials studying the safety and efficacy of opioid painkillers revealed any differences in how the sexes respond after controlling for all other variables? Have any trials suggested that women are more susceptible to the addiction potential of opioids than men?
 - b. If women have not been adequately represented in clinical trials, what steps are in progress to ensure that the provisions of the 1993 law will be enforced?

2. Are there any clinical studies that evaluate whether women have a different dose-response relationship that may impact opioid drug efficacy or increase susceptibility to opioid

⁷ <https://www.drugabuse.gov/publications/research-reports/substance-use-in-women/sex-gender-differences-in-substance-use>

⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858865/pdf/nihms179775.pdf>

⁹ <https://www.nlm.nih.gov/medlineplus/ency/article/007313.htm>

¹⁰ <http://www.apicareonline.com/wordpress/wp-content/uploads/2012/09/04-Editorial-3.pdf>

¹¹ <https://www.congress.gov/bill/103rd-congress/senate-bill/1>

¹² <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126340.htm>

¹³ Ibid.

¹⁴ <http://www.gao.gov/assets/680/673276.pdf>

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addiction? If so, how does this influence the labeling, dosage, and dose interval recommendations provided for a given drug that shows men and women respond differently?

3. Following adoption of the 'Demographic Rule' requiring tabulation of clinical trial participants by age group, gender, and race, has the data generated from compliance with the rule been analyzed by the FDA or clinical trial sponsors in a manner that has impacted decisions for new drug approvals? If so, how?
4. If an opioid drug results in an adverse event for a clinical trial participant, how is the information captured, reported, and used to understand the responses in men verses women?

Thank you for addressing these concerns. If you have any questions, please have a member of your staff contact Avenel Joseph or Elyssa Malin at 202-224-2742.

Sincerely,



Edward J. Markey
United States Senator