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March 7, 2014

The Honorable Margaret Hamburg
Commissioner
U.S. Food and Drug Administration
Rockville, MD 20687

Dear Commissioner Hamburg:

The meteoric rise in addiction to heroin and prescription drugs over the past decade is catastrophic. And the magnitude of the resulting harm that our communities have seen is nothing short of an epidemic. Drug overdose deaths, fueled by prescription painkillers, now surpass homicides and traffic crashes in the number of injury deaths in Massachusetts and in America.[1,2] Approximately 100 Americans die from an overdose every day.[3] And deaths from overdose are just the tip of the iceberg in terms of costs to society. For every unintentional death from opioid pain medications, 9 persons are admitted for substance abuse treatment, 35 visit emergency departments, 161 report drug abuse or dependence, and 461 report misuse of opioid analgesics.[4] This is a true public health emergency that requires a concerted effort from the federal government and public health officials.

The Food and Drug Administration (FDA) plays a critical role in addressing this public health emergency, not only by ensuring that appropriate abuse deterrent mechanisms and monitoring are put into place for marketed prescription painkillers, but also by supporting the development and approval of more medication-assisted treatment (MAT) options for opioid and other addictions. However, given the severity and magnitude of this public health emergency, I am concerned that there are currently too few MAT options available.

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[1] MA 2009: 2,920 total injury deaths; 2034 unintentional injuries; 767 unintentional poisoning/overdose deaths; 599 unintentional opioid overdose deaths; 347 unintentional MVA deaths; 180 homicides. 2009 Injury Data Book. http://www.mass.gov/eohhs/docs/dph/injury-surveillance/injury-surveillanceinjury-report-09.pdf

[2] US 2010: Drug overdose was the leading cause of injury death in 2010. Among people 25 to 64 years old, drug overdose caused more deaths than motor vehicle traffic crashes. CDC Drug Overdose in the United States FACT SHEET. http://www.cdc.gov/homeandrecreationalsafety/overdose/facts.html CDC.2010 Overdose Analysis: 38,329 drug overdose deaths (intentional and unintentional); CDC Injury Deaths: unintentional MVA (33, 687), all homicide 16,259, homicide firearm 11,078.

[3] CDC Press Release: Opioids drive continued increase in drug overdose deaths. February 20, 2013. Total drug overdose numbers: 38,329 in 2010; 60% of these related to prescription drugs including opioid pain medications. http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html

[4] MMWR CDC Grand Rounds: Prescription Drug Overdoses. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6101a3.htm

Furthermore, I am concerned that even a *perceived* focus by FDA on treatments that only result in full cessation of drug use (abstinence) limits the engagement of developers/industry on a broader portfolio of treatment options. Without clear signals from FDA that the agency views measures of improvement or harm reduction as evidence of effectiveness or efforts by FDA to collaboratively engage with industry to establish such measures, drug developers are unlikely to pursue these pathways. Clear guidance on acceptable endpoints and approval pathways is needed to lead drug developers to invest in the R&D for therapies that reduce the consumption of drugs or reduce the harms associated with ongoing consumption of drugs. These may include measures related to craving relief, improvements in other client-reported symptoms, or reduction of harms such as incarceration, family instability, or difficulties maintaining employment.

FDA has a strong history of approving medications for other illnesses, such as depression, anxiety, and other mental health conditions, based on improvement in the severity of symptoms and the daily function of patients versus a total elimination of all symptoms and a complete return to full function[5]. The accepted endpoints and approval pathways that allow for reduction in symptoms and functional limitations appear to have resulted in an expanded pipeline and increased number of approved medications for mental health conditions. Applying similar concepts and standards to substance abuse and engaging on these concepts in a predictable manner may help encourage drug developers to invest in new and innovative solutions for substance abuse treatment.

As the science of harm reduction for addiction may be at a more preliminary stage, development of true partnerships and consistent communications that span the science of public health, clinical trials, regulation, and production are critical to advancing the field. FDA has direct experience participating in such partnerships for emerging issues, for example, with HHS's Biomedical Advance Research and Development Authority (BARDA) for the development of medical countermeasures for public health threats. BARDA brings together CDC, NIH, FDA, and the private sector for an integrated, systematic approach to the development of new interventions.

The suffering and costs of prescription opioid and heroin addiction in this country cannot continue. In light of this and to understand better the role of FDA in developing solutions to this

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[5] For example, "FDA Guidelines for the Clinical Evaluation of Antidepressant Drugs" as far back as 1977 highlight the desire to examine not only prevention and reduction of rehospitalization and use of established rating scales for psychopathology and mood, but also the need to establish measures to assess familial and marital function, social effectiveness, and vocational performance. This signaled to industry the need to collaboratively establish reliable measures beyond suicide and hospitalization and the intent to utilize these measures as part of the evaluation of effectiveness of drugs.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071299.pdf

public health crisis, I respectfully ask that you respond to the following questions by **April 4, 2014**.

1. How many medications are currently approved to treat opiate addiction[6]? Which of these have been approved during the past 10 years? Which of these were approved based on demonstration of effect by harm reduction measures[7]? Please share specific information on what harm reduction measures were used as indicators of effectiveness. To the extent possible, please comment on any new opiate addiction harm reduction products currently in the development pipeline. What drugs have been approved to reduce harm from other addictions[8]?

2. What is the status of regulatory review for nasal naloxone for the indication of opiate overdose reversal? What is the projected timeline for approval? Does FDA view approval as a high priority? If yes, what actions is the agency taking that reflect this urgency? If not, why not? To the extent possible, please comment on outstanding issues, concerns or data gaps that are delaying approval. To what extent have you engaged with other federal agencies on this review?

3. What is the current state of regulatory science for addiction, specifically what are the accepted measures of effectiveness and harm reduction? What regulatory endpoints or pathway(s) for opiate harm reduction treatments have been defined to allow for the evaluation and approval of medications that reduce but do not eliminate use, or reduce the harms from ongoing use? What engagement does the FDA have with developers to communicate the standards of harm reduction for therapeutic approvals? What further resources, in funding or expertise, are needed to accelerate the science of harm reduction and the definition of associated regulatory pathways for opiate addiction?

4. What lessons from effectiveness endpoints and approval pathways for the mental health treatments that result in reduction of symptoms and severity of disease, rather than cure of disease, have been or could be applied to the development of approval pathways other than 'cure' or 'abstinence' for opioid addiction? For other addictions? What are the

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[6] For this letter, "opiate addiction" refers to addictions related to use of prescription opiate pain medications as well as use of non-prescription illicit drugs such as heroin.

[7] For this letter, "harm reduction outcome measures" refers **to products that reduce the consumption of drugs or reduce the harms associated with ongoing consumption of drugs**. These may include measures related to craving relief, improvements in other client-reported symptoms, or reduction of harms such as incarceration, family instability, or difficulties maintaining employment.

[8] For this letter, "other addictions" refers to addictions related to illicit drug use such as marijuana, cocaine, methamphetamine, as well as those related to legal drug use, such as nicotine and alcohol.

concerns, if any, of applying such lessons from the development of mental health treatments to that of addiction treatment?

5. How many staff does the FDA have with specific addiction **and harm reduction** expertise within the Division of Anesthesia, Analgesia, and Addiction Products? Does FDA perceive a need to expand upon these staffing levels and expertise?

6. Development of a pipeline for innovative products to address this high priority public health issue requires true partnership—concerted efforts and procedures to support communication, clarity, and consistency—between public health, clinical research, regulatory authority, and private sector development. What steps has the FDA taken to cultivate this type of partnership for addiction treatments, including those for harm reduction? Has the FDA engaged with the Centers for Disease Control and Prevention, National Institutes of Health, Substance Abuse and Mental Health Services Administration, and/or any non-governmental researchers on the topic of harm reduction for opioid abuse? If so, please provide the dates of such formal meetings, the agendas any whitepapers and participation of such meetings? If not, why not? Please describe any future plans the FDA has to continue and/or expand on such engagement.

7. FDA is a key participant and active partner in development of medical countermeasures under HHS's BARDA. Are there any lessons that the FDA has learned through the BARDA partnership that would be applicable to the development of medical countermeasures for addiction, including those that provide partial protection or harm reduction?

Thank you for your assistance and cooperation in responding to this request. Should you have any questions, please have your staff contact Dr. Shannon Hader or Dr. Avenel Joseph of my staff at 202-224-2742.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator

Cc:
Kathleen Sebelius, Secretary, U.S. Department of Health and Human Services
R. Gil Kerlikowske, Director, White House Office of National Drug Control Policy