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February 6, 2014

Margaret Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Hamburg:

I write to express my growing concern over recent trends related to the approval of drugs, as well as the classification of devices by the Food and Drug Administration (FDA). While I recognize the FDA has made improvements in meeting performance goals for new drug applications and biologic license applications, as outlined in a March 2012 Government Accountability Office report, "Prescription Drugs: FDA Has Met Most Performance Goals for Reviewing Applications," major improvements are still needed to ensure the safety and efficacy of all medical products.

Currently, there are six FDA approval mechanisms designed to address unmet medical need, some of which are based on clinical trials involving relatively small numbers of patients. Last year, the FDA began discussing an *Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need.* Under these new guidelines, the FDA lowers the standard from two well-designed controlled clinical trials to one smaller study that may not necessarily measure a meaningful health outcome. In addition, if the FDA permits smaller sample sizes, it would not be feasible to conduct subgroup analyses for safety and efficacy in women and men, in different racial and ethnic groups, or across age. It would also not be possible to determine the appropriate dosages for these different groups. This information is essential for prescribers and patients.

In addition, for many drugs and devices that the FDA approved based on surrogate endpoints and clinical trials involving small numbers of patients, the FDA failed to require that post-market study results be made public on the FDA website. As a result, patients, physicians, and other health care providers have no objective information about the long-term safety or effectiveness of those products. It is critical that the FDA be direct and transparent about its enforcement mechanisms and penalties when post-market studies are not conducted in a timely manner or do not provide meaningful data about safety or efficacy.

Clinical trial endpoints that prioritize clinically meaningful patient outcomes and methodological targets above surrogate markers of disease are the key to ensuring public health and drug safety. For example, such prioritization was not followed by the FDA when it approved the drug bedaquiline (Sirturo) for treatment of multi-drug resistant tuberculosis (TB) under the agency's accelerated approval pathway. The drug was approved on the basis of a surrogate endpoint — how quickly TB bacteria were cleared from patients' sputum — rather than improved health and wellness for patients.

Considering the small number of patients with multi-drug resistant TB in the United States, instead of approving the drug, availability through compassionate use would appear to be a more reasonable approach to accessibility. Ultimately, the most clinically meaningful evidence from the single small study on which FDA approval was based showed patients were five times as likely to die if they took Sirturo in addition to standard tuberculosis drugs, as compared to standard tuberculosis drugs alone. This was reported in the *Journal of the American Medical Association* and subsequently stated in the drug's black box warning. In light of the fact Sirturo was tested in a randomized control clinical trial, it is unreasonable to assume, absent definitive evidence to the contrary, that the increase in death happened by chance or was not due to the drug.

Regarding medical devices, I am disappointed to note that the FDA is using a provision of the Food and Drug Administration Safety and Innovation Act to down-classify most high-risk pre-amendment devices. Although the FDA proposed keeping several of the devices at Class III, in most cases the identical device is down-classified to Class II for some indications, virtually ensuring that most manufacturers will use the faster, less stringent 510(k) review process, rather than the premarket approval (PMA) process. For example, at the end of December, the FDA issued final orders for split classifications for two life-saving cardiovascular devices, the Intra-Aortic Balloon and Control System and an External Counter-Pulsating device. As Class II devices, these high-risk and life-saving devices are not required to be proven reasonably safe and effective in clinical trials, nor are their manufacturing processes inspected prior to putting these devices on the market. Cardiologists have pointed out that this could be life-threatening to patients.

In addition to the general concerns outlined above, I would like to request the following information:

- What enforcement mechanisms and penalties is the FDA using when post-market studies are not conducted in a timely manner or do not provide meaningful data about safety or efficacy?

- Considering the small number of patients with multi-drug resistant TB in the United States, instead of approving Situro, why didn't the FDA ensure that the drug was made available through compassionate use while the drug is tested further to ensure it is not deadly?

- In the President's Council of Advisors on Science and Technology September 2012 "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation," from which the *Alternative Approval Pathway* was derived, the Council explained that such a pathway would be ineffective without overhauling the FDA's approval and regulatory

processes to protect patients. What changes does the FDA already have authority to make in order to improve this process and what has your agency done to exercise this authority?

- Please provide a list of all devices that have split Class II/Class III classifications
    - Provide data comparing how often within the last ten years that companies with devices that have split classifications have submitted a PMA for the Class III indication
    - How often have companies submitted a 510(k) application?
    - Provide any analysis that the FDA has conducted to determine if the split classification devices cleared through the 510(k) process are promoted or sold for the Class III indication.

Thank you for your prompt attention to this critical public health issue. I look forward to your response to these concerns and to our continued work together to ensure the safety of the drugs used to treat American patients.

Sincerely,

Rosa L. DeLauro

Rosa L. DeLauro
Member of Congress