Questions for the Record from Senator Braun

1. The FDA has supported fully modernized paper prescribing information since 2014 but has been blocked from moving forward by an appropriations rider since 2015 even though nearly all prescribers consult the real-time digital version on the National Library of Medicine's DailyMed website to best serve their patients. The Environmental Paper Network calculates that the continuation of the paper requirement equates to the unnecessary consumption of 12 million trees annually and is the greenhouse gas equivalent of adding 816,000 new cars to our roads each year. If confirmed, would you support reopening the public discussion about electronic labeling of prescribing information to enable prescribers to focus on the most up-to-date information for their patients, and to eliminate this senseless waste?

Response: This rule was proposed to help ensure that the most current prescribing information is publicly accessible for the safe and effective use of human prescription drugs. At the time of publication, the Agency encouraged patients, health care providers, and other stakeholders to submit comments to the docket for this proposed rule, with information or data supporting their concerns.

In addition, in the preamble to the proposed rule, FDA requested public comments on aspects of the proposal, including whether alternatives to request a paper copy of the prescribing information are adequate, and on alternative distribution systems in which both paper and electronic prescribing information would be available. I am also aware that under the 2021 Consolidated Appropriations Act, the Agency is prohibited from taking any action with respect to allowing or requiring information intended for a prescribing health care professional to be distributed to such professional electronically (in lieu of in paper form) unless and until a Federal law is enacted to allow or require such distribution.

2. To what extent are you, as incoming FDA Commissioner, committed to addressing the continued need to evolving trial design and approaches to bringing new products to market? Pilot programs like the Model-Informed Drug Development program offer manufacturers and the Agency an alternative approach to bringing to market an otherwise challenging product to study. How will you integrate these types of programs as a permanent part of the FDA approach to drug development in your tenure?

Response: If confirmed, I am committed to ensuring that product development and review is completed in the most efficient way possible to ensure the Agency gets to the critical questions of safety and efficacy of products. This includes integration of methods from pilot programs, like the one you mentioned, if they prove to improve clinical trial efficiency, enhance the probability of regulatory success, and optimize other aspects of drug development.

3. Digital health technologies, which can encompass wearables, sensors and software technologies are being developed in large numbers and have the potential to impact patient unmet need. The role of the FDA in validating and approving these

technologies is critical to provider and patient acceptance, how will you modernize the Agency's approach to these types of technologies to create a transparent and predictable process for approval? Will you commit to also providing education on the products and approval approach to help drive consumer and HCP awareness?

Response: As you know, I am very interested in supporting responsible development of safe, effective digital health technologies for patients in the U.S., and I look forward to working within the Agency to support its efforts to bring new digital health advances to patients in as timely a manner as possible, while also ensuring patients can still depend on them. As I mentioned during my confirmation hearing, I am highly supportive of the efforts of FDA's Digital Health Center of Excellence, and see it as an important way to empower stakeholders to advance health care by fostering responsible and high-quality digital health innovation, including for software-based medical devices. I am looking forward to working within FDA on these efforts as they are important to applying a comprehensive approach to digital health technology to realize its full potential to empower consumers to make better-informed decisions about their own health and provide new options for facilitating prevention, early diagnosis of life-threatening diseases, and management of chronic conditions outside of traditional care settings.

4. Earlier this year my Colleague Sen. Booker and I introduced a bipartisan bill to convene a White House Conference on Food, Nutrition, Hunger, and Health. Our legislation included in its findings "diet-related diseases greatly worsen outcomes from COVID-19".
    a. As you noted in a recent journal publication, COVID-19 has caused a "tsunami" of unintended consequences with respect to patient health and the treatment of common chronic diseases, particularly cardiometabolic diseases, largely due to patients not being screened for things such as elevated cholesterol at the rate in which they should. As a cardiologist, what recommendations do you have for the Committee in terms of steps the government can take to improve the frequency of screenings and treatments for patients to reverse this concerning trend?
    b. What steps should the FDA consider to encourage greater innovation and flexibility in the development of new, innovative therapies to improve the treatment of cardiovascular disease, which we know is the leading cause of death in the Unites States annually and which is unfortunately increasing once again after years of decline?

Response: Throughout my career, I have seen the effects of heart disease and obesity, and the decade long decrease in life expectancy in the U.S. is driven by a growth in common, chronic disease that is impacted by dietary habits and amenable to better screening and intervention with an array of effective therapies, many of which are generic and inexpensive. It is apparent that the current pandemic has amplified the need for improved nutrition, given the increased risk for severe symptoms and death from COVID-19 for those with obesity and other chronic conditions. FDA's policies regarding nutrition have advanced since I was last at the Agency, and if confirmed, I am committed to prioritizing food and nutrition issues to realize measurable impacts on preventable, chronic diseases. In conjunction we also need to stimulate the biomedical science

and industry communities to develop new approaches to diagnostic tests and therapeutic interventions to stem this "tsunami" of common, chronic disease and I look forward to working with you on this topic.

5. The FDA has played a major role in the development of new treatments for cancer. Part of this progress relates to a successful effort to streamline the development of cancer therapies through cross-center collaboration and common standards for Breakthrough and Fast Track designation. Given the dual crises of opioid related overdose deaths and the need for relief of chronic pain by tens of millions of Americans would you commit to implementing a similar approach to spur the development of effective, safe, non-addictive treatments for pain?

Response: I commit to using all the tools available to FDA to aggressively address both the overdose crisis and the lack of alternatives to opioids for treating pain.

I am committed to reviewing all aspects of FDA's role in combating the addiction and overdose crisis during my first year if confirmed, including how to encourage industry to invest more in non-addictive pharmacological treatments and strengthening collaboration with NIH and other government agencies to advance the development of non-addictive pain treatments. Despite past efforts, current evidence shows that we have not done enough to combat the opioid epidemic, and if confirmed, I am committed to working with you to identify any potential areas that might benefit from congressional action.

6. Congress is currently considering legislation to modernize how diagnostic tests are reviewed and approved by FDA. The VALID Act would help incentivize and speed innovation of safe and accurate clinical diagnostic tests, by creating a modernized, predictable, and risk-based regulatory framework for all diagnostic tests, regardless of where developed. The pandemic has shown the particular importance of innovative and accurate diagnostic tests, and the need for transparency for patients and clinicians to know which tests are available and how well those tests perform.
    a. Will you work with this Committee to refine and advance the VALID Act?

Response: Yes, I strongly support the need to create a modern framework for oversight of all in vitro diagnostic tests. I look forward to working with the Committee to ensure any legislation strikes the balance needed to promote innovation and development of diagnostic tests, including for unmet needs, while adequately protecting patients and the public health.

7. Dr. Califf, I would like to ask you about change control plans. FDA has proposed the use of such plans in the artificial intelligence space, but there is a lot of interest in making this novel concept more widely available across FDA. In brief, a change control plan allows developers to anticipate changes in a product over time and submit those to FDA for approval along with a premarket submission. Should FDA approve that plan, the developer could make a change within the scope without

requiring a new submission to FDA. This concept is particularly helpful in the digital health space, given the iterative nature of these products.

To give just one example, right now the developer of a regulated app must frequently make two submissions for the same app to FDA in order to provide the app through both the iOS and Android platforms. Using a change control plan, and with FDA's approval, we could maintain our high standards for safety and efficacy and also make an updated digital product available to the end user more quickly.

a. Would you be supportive of expanding access to change control plans beyond the artificial intelligence and machine learning space?

Response: As you know, I am very interested in supporting responsible development of safe, effective digital health technologies for patients in the U.S., and I look forward to working to see how we can continue to bring new digital health advances to patients in as timely a manner as possible, while also ensuring patients can still depend on them. I am highly supportive of the efforts of FDA's Digital Health Center of Excellence, and see it as an important way to advance healthcare by fostering responsible and high-quality digital health innovation, including for software-based medical devices. Transparent and effective change control plans are critical to reliable production of devices that are safe. I am looking forward to working within FDA on these efforts as they are important to applying a comprehensive approach to digital health technology to realize its full potential to empower consumers to make better-informed decisions about their own health and provide new options for facilitating prevention, early diagnosis of life-threatening diseases, and management of chronic conditions outside of traditional care settings.

8. The FDA's Oncology Center of Excellence has led the agency's embrace of innovative clinical trial designs and utilization of statutory programs like Breakthrough Designation and Accelerated Approval to speed new therapies to patients that lack other treatment options, including those with rare cancers. However, the agency's embrace of these regulatory flexibilities for other rare diseases is much further behind. For rare diseases, even those with extremely limited patient populations, the agency is inconsistently applying the programs and flexibilities Congress established to help facilitate the development of safe and effective therapies. As Commissioner, do you commit to working across the Center for Drug Evaluation and Research to provide greater clarity about how regulatory flexibilities for rare diseases should be applied to provide patients and product developers greater certainty?

Response: Throughout my career, both at FDA, and as a practicing clinician, teacher and researcher, I have seen first-hand how the rare disease community has demonstrated the power of patient advocacy. Patients and families, working with the clinical and research communities, have created an extraordinary and disciplined movement to get information and seek answers, to stimulate research and generate the evidence needed to develop treatments with the goal of helping their loved ones with a rare disease have a better and longer life.

During my previous tenure as Commissioner, I learned how FDA works collaboratively with many people and stakeholder groups to support rare disease product development, including patients, caregivers, and drug and device manufactures. Despite the fact that 58% of new molecular entities approved in 2020 were to treat rare diseases, rare disease drug development continues to be a challenge and thousands of diseases do not yet have an effective treatment. I am encouraged, however, that the revolution in biomedical knowledge on many fronts has advanced our understanding of disease mechanisms. Additionally, innovations in trial design and conduct give us the ability to generate high quality evidence about the benefits and risks of therapies in development. Given the importance of accelerated pathways for rare diseases, the post-market phase deserves particular attention to ensure that we understand the long-term effects of interventions, and the new tools made possible by digital technologies and electronic health records should enable a much more thorough evidence base for effective treatment. I commit to working with the experts at FDA to leverage these advances and the work that has already been done to get life-saving therapies and treatments to patients with rare disease. If confirmed, I look forward to continuing these efforts to meet patient needs.

9. As you know, CDRH and the device industry are negotiating MDUFA V, which will determine the amount of user fees that the device industry is required to pay FDA over the next five years. Based on media reports, CDRH has asked the industry to pay for the costs and expenses at CDRH that are not related to the premarket review of device submissions and is asking industry to pay in excess of $2.4B in new fees - a nearly 2.5 increase in fees from the current agreement. Furthermore, CDRH's proposal is not tied to any commitments to enhance performance. In sum, CDRH is suggesting that they need 2.5 times more funding to deliver on the goals agreed to nearly five years ago under the current user fee agreement.

   I would also note that the amount FDA is seeking would undermine the foundational principle of the MDUFA program which is that congressional appropriations are the primary source of funding and industry user fees are additive to enhance the premarket review program.

   a. What will you do as Commissioner to reign in CDRH with regard to its proposed spending and budgeting of MDUFA funds?

Response: MDUFA V is still under active negotiation between FDA and industry. Since I am not yet at the Agency, I am not privy to those negotiations. The consideration of performance of user fee commitments is a key factor in the user fee reauthorization cycles. If confirmed, I look forward to working closely with this Committee on the MDUFA V reauthorization proposal to assure the agency is resourced to speed the development and approval of safe and effective medical products.

10. I continue to hear from the medical device industry that CDRH’s requirements regarding biocompatibility are unduly burdensome and that the requirements are disproportionate with the risk involved. CDRH asks companies for more biocompatibility testing, more often, for no clear reason. How can we ensure that

these requests are risk-based and tied to a scientific "need to know", as opposed to an academic "nice to know"?

Response: I share your interest in ensuring that evidentiary requirements for marketing medical devices and other products are risk-based and ensure patients have timely access to the newest advances when they meet FDA's standards. I pledge to take a closer look at this and look forward to working with you to ensure that FDA is enabling U.S. patients to have timely access to safe and effective medical devices in a timely manner and fulfilling the Agency's obligations to review submissions in the least burdensome manner possible.

11. COVID has been front and center in health care for over 20 months. But in that time, development of novel cures and treatments has not stopped, especially in cancer where patients are desperate for new options.
    CBER received additional funding this year.
    a. How will you use that funding to ensure efficient reviews managed by staff with the necessary background and expertise to understand the novel therapies in front of them?
    b. Particularly for therapies with RMAT designation, how will you ensure that reviewers have the expertise appropriate for this breakthrough therapies?

Response: If confirmed, I look forward to ensuring CBER is appropriately staffed with reviewers with the appropriate expertise, for breakthrough therapies and other innovative products. This expert staff is critical to facilitating and expediting development of medical countermeasures and ensuring that FDA continues to have the expertise to keep up with the most urgent needs. CBER's funding can also be used for enhancing technological infrastructure to enable more rapid responses in the future. I would look forward to working with CBER to address the critical needs to ensure appropriate review of novel therapies.

12. FDA's "emerging signals" policy—where FDA issues safety communications about medical devices before actually validating that a safety issue exists—leads to confusion for physicians and patients not getting needed care. Part of what's frustrating about this policy is that FDA doesn't regularly revisit or update these "signals" as new information becomes available. How do we ensure an appropriate balance of FDA communicating known safety concerns but also not scaring people needlessly? How can we ensure that information is updated on a regular basis? How can we make sure that industry is part of the discussions prior to a signal being issued?

Response: While an emerging signal does not mean FDA has definitively concluded that there is a causal relationship between the medical device and the emerging signal, providing consumers with access to the most current information on potential benefits and risks of marketed medical devices allows patients and clinicians to make informed decisions about their treatment and diagnostic options. FDA works collaboratively with manufacturers to evaluate safety information and coordinate public messaging. We also need to bolster our post-market evidence generation

system to reduce uncertainty about these signals. FDA does provide updates to safety communications when there is significant new information to share related to the emerging signal.

13. Over the last several years, this committee has heard from the animal feed industry of concerns with the slow pace of reviews within the Center for Veterinary Medicine for new feed and pet food ingredients. We addressed a few inefficiencies during the last ADUFA reauthorization and with some dedicated appropriations in fiscal year 2020. More needs to be done so our livestock producers can get access to new feeding technologies that can allow them to compete globally. Are you aware of these concerns and can you commit to addressing them?

Response: Thank you for raising this important issue. FDA's review of new animal food ingredient submissions helps ensure that innovative food ingredients are safe for animals, while also ensuring that the meat, milk, and eggs from those animals are safe for people to eat. This industry is evolving and developing innovative new animal food ingredients that result in complex submissions to the Agency. I am committed to working with stakeholders to continue to address their concerns.

14. There is also a need for CVM to modernize the method of regulating some feed ingredients that have the potential to greatly impact animal production, food safety and the environment. The Policy and Procedures Manual Guide 1240.3605 has not been updated since 1998 and regulates ingredients making production, food safety or environmental claims as animal drugs instead of a feed ingredient. Research has shown that some animal feed ingredients can reduce greenhouse gas emissions in livestock; however, these ingredients are currently regulated as new animal drugs and therefore are not being brought to market in the U.S. Other countries are approving these ingredients leaving our livestock industry behind in their ability to use animal nutrition to meet their climate goals. We need your assistance getting this policy modernized and these ingredients regulated as feed ingredients when they act within the digestive tract and its contents.

Response: If confirmed, I will commit to taking a close look at this issue. I'm aware of the increasing interest in novel animal food ingredients being a tool to improve production or reduce greenhouse emissions. I share your goal that FDA needs to find the right balance between appropriate regulation while not slowing down innovation in the animal food sector.

15. In recent weeks, several press articles have pointed out the struggles in the U.S. to bring new feed ingredient products to market that can help improve environmental outcomes. They note that the FDA wants to regulate these products as animal drugs instead of as a feed ingredient. What will you do as Commissioner to see that these products are regulated as feeds and reviewed quickly? We don't have 10 years to wait

when we need to be meeting our global commitment on reducing methane emissions by 2030.

Response: If confirmed, I will commit to taking a close look at this issue. I'm aware of the increasing interest in novel animal food ingredients being a tool to improve animal production or reduce greenhouse emissions. I share your goal that FDA needs to find the right balance between appropriate regulation while not slowing down innovation in the animal food sector.

16. Dr. Califf, I am excited about the potential benefits animal biotechnology can provide to our farming and food systems by improving animal and human health, fostering resiliency, and sustainably increasing protein and dairy production. Unfortunately, the FDA's current regulatory approach to the technology is keeping these beneficial technologies from coming to market or shift overseas to countries with more predictable commercial pathways. This summer, the American Association of Veterinary Medical Colleges (AAVMC) and the Association of Public and Land-grant Universities (APLU) available here recommended USDA and FDA "come together and shape a harmonious, transparent, evidence based, and forward-looking regulatory process in step with the current scientific progress."
    a. Will you commit to FDA working with USDA and the White House to develop an efficient, risk and science-based regulatory system that can create a safe, predictable path to market for these critical innovations?

Response: From my time previous tenure at FDA, I know that the Agency works closely with other U.S. government agencies on a variety of matters. If confirmed, I am committed to working with USDA and other federal and state partners on this issue.

17. Dr. Califf, over the last few years, the U.S government has made significant progress in modernizing the coordinated framework for the oversight of agricultural biotechnology. In particular, addressing products of new techniques like gene editing. USDA and EPA have taken positive steps, but to date FDA has not taken any public actions to update its oversight role.
    a. Can you commit to leading FDA to also review and modernize its approach to agricultural biotechnology, so that the U.S. government provides a unified, consistent approach to products of new technologies like gene editing?

Response: From my time previous tenure at FDA, I know that the Agency works closely with other U.S. government agencies on a variety of matters. If confirmed, I am committed to working with USDA and EPA on this issue.

18. Health tracking devices, like Continuous Glucose Monitors, Owlet Smart Socks, iWatches and more, offer the opportunity for Americans to monitor important bodily functions on a day-to-day basis.

a. Do you believe that any, or all, fitness and health trackers should receive FDA approval? What statutory authority or flexibility mandates or provides for FDA jurisdiction related to such approval?

Response: I share FDA's goal of applying a risk-based approach to its regulation of medical devices, including digital health technologies, and the Agency has been clear in its implementation of Section 3060(a) of the 21st Century Cures Act (Cures Act) that general wellness software functions that are used solely for fitness and health tracking purposes and present a low risk to the safety of the user do not meet the definition of a device under section 201(h) of the FD&C Act, as amended by section 520 of Cures, and therefore are not subject to the FD&C Act's regulatory requirements for devices. As you know, the area of digital health is one of my great interests and I look forward to helping U.S. patients have access to the newest innovations in this area and ensuring patients can depend on them to provide accurate, reliable and interpretable information, particularly when their intended use goes beyond general wellness health and fitness tracking.

19. As you are well aware, during your tenure as FDA commissioner, the FDA loosened standards governing use of the abortion drug mifespristone. From 2000 to 2018 alone, this abortion pill has taken more than 3.7 million preborn lives, caused 24 maternal deaths, and resulted in more than 4,100 adverse maternal reactions including hemorrhage, excruciating abdominal pain, and severe life-threatening infections.[1] **If confirmed, will you rescind FDA's temporary halt of enforcement of the regulation requiring that the abortion pill be administered physically in person by a clinician?**

Response: On December 16, 2021, after conducting a review of the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, FDA determined that the data supported modification of the Mifepristone REMS Program to remove the in-person dispensing requirement. The agency further added a requirement for pharmacy certification. Prescriber certification and patient counseling on the appropriate use of the drug are still required under the REMS. I have confidence in the FDA staff, who rely on the latest evidence, to make the right decision on these matters. If I am confirmed, I will ensure the Agency continues to monitor the safety of this and all other approved drugs.

20. The issuance of warning letters can devastate the reputations of companies, even those that are actively seeking to comply with existing FDA regulations in good faith.
    a. Do you believe the FDA should communicate with a company prior to issuing warning letters and/or work with them to correct mistakes that were made inadvertently and did not put consumers at risk?
    b. What role do you believe warning letters serve?
    c. Should you be confirmed, what, if any, changes would you seek to implement related to the issuance of warning letters?

[1] https://www.ansirh.org/sites/default/files/publications/files/mifepristone_safety_4-23-2019.pdf

Response: From my previous time at FDA, I know that warning letters are an important tool that FDA uses to achieve voluntary compliance and provide notice of violations of law. If a firm believes that its products are not in violation, it can respond to the letter with its reasoning and any supporting information for FDA's consideration. Warning Letters give firms an opportunity to voluntarily correct the violations. Firms are generally provided time to respond and bring their products and/or facility into compliance, and FDA works with firms towards achieving that goal. I am aware that a trade-off of this tool is that it can negatively impact the public perception of firms. If confirmed, I'd look forward to hearing more about your perspective on this issue, and whether you believe any changes should be considered.