## Questions for the Record from Senator Marshall

1. Like you, I also support improving the collection and utilization of real-world evidence at the FDA. My bipartisan legislation – the FDA ACTS Act (S.1508) – would have the FDA better leverage real-world evidence when assessing the safety and effectiveness of medical devices, biologics, and drugs. As you know, makers of medical technologies, vaccines, and therapeutics that have received EUAs are ramping up their applications to get full approval.
    a. As Commissioner, how will you work with manufacturers to get data in a manner that will best inform the FDA centers in giving them the stamp of approval?

**Response**: During my last tenure as Commissioner, I helped lead the agency forward toward more widely using real-world evidence (RWE) in its regulatory decision-making processes. I can assure you that, if confirmed, I will continue this trend, including evaluating all evidence, including RWE, for products that have received EUAs as they work toward full clearance or approval.

Real-world data (RWD) and RWE have great potential value in informing regulatory decision making. We have a labyrinth of information that needs to be knitted together so that we have information in as close to real time as possible. We have seen an approximation of this with the COVID tracker that shows us almost in real time the number of cases, the hospitalization rates and the death rates.

If I am confirmed, it will be part of my agenda to get additional RWD-related regulatory policies and systems in place, and to give people confidence that it is in their interest to use RWD in support of medical product development. But for that to work, we need to have the policies right. FDA should continue considering RWD/RWE that is fit-for-purpose and meets scientific and regulatory standards. The utility of data to permit appropriate inferences regarding the safety and effectiveness of a medical product will depend on multiple factors, including the quality and extractability of the data, the ability to use such data in an appropriately designed study using appropriate statistical and epidemiologic methods, and accounting for problems regarding how consistently a disease is diagnosed and treated as well as the heterogeneity of the study population.

I am aware that the Agency has several initiatives ongoing to continue to explore the use of RWD and RWE in regulatory decision making, and there have been some great results from these efforts already. For instance, the Agency published a report in March 2021 with 90 publicly available examples where RWE was leveraged to help make regulatory decisions on a wide range of medical devices. RWE has also been used in recent drug approvals. In addition, the agency has just released four draft guidances on use of RWE in drug development. I look forward to working to continue to build upon these ongoing efforts and working with manufacturers to get this data and would look forward to working with you on an improved post-market evidence generation system if confirmed.

2. As you know, CERSIs are collaborations with academic institutions to advance regulatory science. Along with a variety of other activities, CERSIs have been used to

assess real world evidence of medical products. While I am a supporter or the agency relying more consistently on real world evidence, I recognize the need for academic institutions to conduct studies and submitting reports that FDA may rely on for regulatory decision-making to be in a manner that meets the same scientific integrity and rigor expected of product sponsors.

a. What policies and standards should be in place to ensure that FDA receives full transparency as well as the underlying data relating to reports and studies that are funded through the CERSI program?

**Response**: These collaborative efforts by FDA and academic institutions can foster a robust, collaborative, regulatory science culture to address the scientific challenges presented by revolutions in medical product development. During my previous tenure at FDA, I saw how important early communication and transparency were for sponsors and our regulatory science collaborators, and I will bring this perspective if confirmed again. That transparency is just as important in the reverse direction—FDA needs accurate data and transparency in the information it receives to make the most appropriate decisions in protecting the public health. I would look forward to engaging in the transparent dialogue in this space to continue making new approaches to evaluating the safety and effectiveness of products possible.

3. In March, I penned an op-ed in the Wall Street Journal, <u>One Shot is Better than None</u>, discussing the use of real-world evidence and how the FDA isn't really being proactive in harnessing data from other countries to make practical decisions during a pandemic. As an example, thousands of seniors here in the US were hospitalized or died over the summer before the FDA finally authorized a booster in the fall.

    a. How can we leverage millions of patient records from other countries during pandemics in making life-saving decisions faster without compromising the gold standard that we're known for?

**Response**: Building a system to curate and use the significant amount of health data stored throughout the country is essential to making decisions quickly. However, this data will not and cannot be used without careful planning for study design followed by high quality analyses being conducted. Well planned studies will allow this data to be used in a way that is conducive to making decisions and upholding FDA's international reputation as the gold standard for regulatory approval. The area of digital patient records is evolving rapidly and I look forward to working with the FDA and the global community to optimize the quality and reliability of this data and to continuing to work with you on this issue if confirmed.

4. Honest science cannot function with a politically predetermined outcome. This pandemic has done enormous harm to our public health agencies and the trust the American people have in them. In September, two senior FDA officials resigned over frustrations with President Biden's plans to recommend booster shots.

    a. What will you do to ensure that the White House does not continue to meddle in FDA affairs and what will you do to help restore Americans faith in our public

health agencies and the medical advice that's being given by them to our citizenry?

**Response**: It is important for the public to be able to trust the FDA's regulation of their food and drugs. We need to work together to build trust where the evidence is solid. As they have been, if confirmed I will work tirelessly to ensure that FDA will continue to make its decisions based on the latest data and scientific principles and to communicate the basis for these decisions in a manner that is understandable and transparent to the public. I trust the FDA career staff to make well-informed decisions based in the science. That would be the same standard if I am confirmed.

5. Throughout the year, Kansans have asked me what the future of coronaviruses will look like. It might look like the flu where testing and therapeutics play major role given how viruses mutate much faster than we can make vaccines.
    a. If we had better t-cell testing that can measure your level of protection, imagine what it could do. Doctors would have better conversations with their patients. We'd better understand prior exposure of infection, the duration of vaccine-induced immunity, and future dosing for specific populations. I've tried to get the FDA to prioritize this type of testing at the level of Operation Warp Speed, but I haven't received a commitment that would usher a wave of this type of tests akin to the results from the Rapid Acceleration of Diagnostics (RADx®) initiative. I understand RADx was an interagency project that involved strong collaboration with experts at the FDA. What are your thoughts?

**Response**: I agree it is essential that the public understands the true value of different types of tests and FDA has an important role in communicating this information to the public. In order to understand the utility of T-cell tests to assess the level of protection provided by an immune response to vaccination, tests need to be specifically evaluated for that use. Further, there needs to be a body of evidence correlating test results with a level of protection. While as a nominee I do not have access to internal, confidential documents from test developers of FDA, research is ongoing in this area and, as of now, it is my understanding that there is no established correlate of protection. Similar to T-cell tests for other infectious diseases, it is not established that the results of T-cell tests can be used to determine an individual's protection from SARS-CoV-2 infection. If these test results are interpreted incorrectly, there is a potential risk that people may take fewer precautions, which can increase their risk of SARS-CoV-2 infection and may result in the increased spread of SARS-CoV-2. If confirmed, I am committed to ensuring we keep the public up to date on the latest science about the use of T-cell tests to evaluate immune response and that the FDA continues to support further research in this area.

The RADx program is an innovative interagency approach to accelerate the review and availability of tests to the public by leveraging government expertise and working hand in hand with companies to compile data to demonstrate performance benchmarks. I am interested in exploring additional uses for this approach to regulation of medical products.

b. On therapeutics, drug repurposing offers a promising route for the development of prevention and treatment strategies for COVID-19. Under your leadership, how can the FDA can play a proactive role in further advancing this effort?

**Response**: During a pandemic time is of the essence in developing vaccines and treatments. It was during my tenure at FDA in January 2017 that the EUA guidance was finalized, which discusses the statutory "may be effective" standard for EUAs. This standard is a different level of evidence than the "effectiveness" standard that FDA uses for product approvals. The guidance also includes discussion of the statutory standard that the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product.

This standard provides flexibility in accelerating the development of therapeutics, including the re-purposing of existing drugs, when data from adequate and well controlled trials support it. The Agency has done that, with Remdesivir for example. FDA still needs to have sufficient evidence to make an assessment of a therapy's potential against COVID-19, while using the flexibilities under the EUA framework to accelerate the development of novel or repurposed therapeutics. I believe that FDA has found the right balance and I would continue the work to do that if confirmed.

6. The CDC describes antimicrobial resistance, or AMR, as "one of the biggest public health challenges of our time." Drug-resistant pathogens directly contribute to hundreds of thousands of deaths annually in the United States, but they can also derail the safe and effective delivery of medical care more broadly for patients receiving chemotherapy, organ transplants, and even those undergoing routine surgical procedures. Furthermore, it's likely that this crisis has been exacerbated by the COVID-19 pandemic. And yet innovation is dwindling in this critical sector, and the antimicrobial ecosystem is on the verge of collapse.
    a. What actions will you take to prioritize our nation's fight against the "silent pandemic" of AMR – and, specifically, to address the crisis in the antimicrobial sector, with a diminishing number of companies working to develop new products to address pathogens that have become resistant to existing drugs?

**Response:** I wholeheartedly agree that antimicrobial resistance (AMR) is a significant and evolving national and global public health issue. If confirmed, I will lead the Agency to support the development of new antimicrobial products as well as support the judicious use of existing antimicrobials in both human and veterinary medicine. Further, I know the Agency is committed to facilitating innovation through the proactive engagement with sponsors and researchers to identify and address challenges to the development of new products.

7. Last Congress, I spearheaded an effort in the House to ensure patient access new chimeric antigen receptor (CAR) T-cell therapies that had just been approved by the FDA. Two therapies approved by the FDA within the last three years reengineer a patient's healthy t-cells to defeat lymphoma and pediatric leukemia. For patients with

non-Hodgkin lymphoma, Yescarta leads to a remission rate of 51 percent. For children with acute pediatric lymphoblastic leukemia, Kymriah demonstrated an 82 percent remission within three months of treatment. I'm proud to say that Kansan patients and my alma mater have played a great role in helping them get to market.

a. Can you please share what you will do as FDA Commissioner to better position the agency to accelerate access to innovative cell and gene therapies and also how the FDA can work with Centers for Medicare and Medicaid Services and National Institutes of Health to reduce the time it takes to move discoveries in personalized medicine from bench to bedside?

**Response:** As you know, cellular and gene therapies are relatively new to the medical field and due to this newness, familiarity with them is not as high as with some other, more established medical products. Therefore, it is FDA's duty to ensure that cellular and gene therapies are properly understood from the regulatory perspective and that applications for approval are reviewed thoroughly, as with all applications that come to the Agency. Continuing to increase the familiarity of FDA scientists with the latest advances in cellular and gene therapy will cut down on application review time and allow for informed decisions to arise more quickly, thus, allowing patients more timely access to treatments. If confirmed, I would support the use of FDA's expedited review authorities, such as the regenerative medicine advanced therapy (RMAT) designation, when appropriate, to help make cellular and gene therapy products that are shown to be safe and effective available as soon as possible. Furthermore, improvement in our post-market evidence generation system should enable continuing assessment of benefits and risks over the duration of impact of these products.

8. I worry about the future of abortion policies under this administration and how politically-appointed officials will use FDA as a political tool to undermine mifepristone's complications and risk levels. Specifically, I shudder to think FDA removing REMS requirements. As you know, REMS requires prescribers to be certified and dispensed in an appropriate setting.

    a. In 2016, FDA decided to continue holding the REMS program where prescribers are certified, and the drug be dispensed in an appropriate setting. Can you ensure to me that you will uphold the 2016 standing?

**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.

9. During the pandemic, FDA suspended enforcement of the in-person requirement for mifepristone, noting it partly relied on the "small number of adverse events reported to the FDA last year. But under your tenure, the FDA changed the mifepristone REMS safety protocol so that severe adverse events were no longer required to be reported – only deaths. During the HELP Committee hearing, you said that you relied on FDA staff in making clinical recommendations. However, FDA cannot make scientific recommendations in clinical appropriateness as it is not collecting all relevant adverse outcomes related to this medical product.

    a. Do you find it clinically appropriate to purposely exclude data collection on adverse outcomes related to medical products including those that have REMS requirements, for the purposes approving and/or making label changes?
    b. Would you be open to reinstating reporting requirements for severe complications from mifepristone-induced abortions?

**Response:** All holders of approved drug applications are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements in FDA's regulations. If I am confirmed, I commit to following the best available science related to this and every matter, and I will ensure the Agency continues to monitor the safety of this and all other approved drugs.

10. Over the past few years, CDER announced a draft guidance titled "Innovative Approaches for Nonprescription Drug Products" that could aid manufacturers and provide greater frequency for the approval of switches, which in many years, only see FDA approve a few applications. Unfortunately, this draft guidance has not resulted in a final rule, which has delayed the ability for these Rx to OTC switches by allowing certain new conditions to ensure safe use. Without this final rule, consumers can not realize the cost savings from Rx to OTC switch and the convenience of the availability of these medicines over-the-counter.
    a. Are you aware of this issue and would you consider prioritizing this guidance?

**Response**: I'm very mindful that if a drug is able to be provided as a non-prescription drug, it facilitates access, and that reducing barriers to access, when appropriate, is important particularly for a drug that must be taken repeatedly for chronic conditions. I am aware of FDA's intent to publish a regulation on Nonprescription Drug Products with an Additional Condition for Nonprescription Use and I will work towards bringing this rule to publication.

11. Truth in food labeling is extremely important, however, the FDA routinely fails to enforce its own standards of identity. The most prime example is milk which is defined as the lacteal secretion from cows. I continue to walk down the grocery isle seeing plant-beverages claiming to be milk. They are not nutritionally similar, but people think they are because those products are called milk. I have no problem with soy or almond beverages. They simply are not milk and shouldn't be called it. Secondly, there are plant proteins that fall under your jurisdiction that are attempting to brand products as meat.

Several studies show that when plant proteins use words like "plant-based" meat consumers believe some portion of the product comes from an animal. These products often hide the disclaimer in hard to find places making it extremely difficult for a consumer to understand if a product is an exclusively plant protein, blended, or a meat product.

a. Do you commit to enforcing your standards of identity, especially as it relates to milk?
b. Do you commit to creating standards of identity for other plant proteins that would prevent such proteins from using nomenclature that is otherwise associated with beef, pork, or poultry?

**Response**: The Agency is working to modernize standards of identity to ensure that food meets consumers' expectations while reflecting current marketplace practices and modern technologies. If confirmed, I will commit to taking a close look at this issue.

12. Over the last several years, this committee has heard concerns from the animal feed industry about 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 provided some dedicated appropriations last year. But, more needs to be done so our livestock producers can get access to new feeding technologies that can allow them to compete globally.
    a. It seems like giving you more monetary resources have not help speed up the process. 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.

13. Last week, Agri-Pulse pointed out the struggles in the US to bring new feed ingredient products to market that are able to reduce methane emissions from cattle. It says that the FDA wants to regulate these products as animal drugs instead of as feed ingredients. There are several other products for animals that do not meet the definition of a "drug" and are more of a dietary supplement or feed ingredient.
    a. What will you do as Commissioner to see that these products are regulated as feeds and reviewed quickly?

**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.

14. I have appreciated FDA's leadership during the pandemic and the agency's ongoing engagement with the food and beverage industries to continue to have food on American's tables. The food industry is experiencing severe supply chain disruptions currently.
    a. How can the agency balance the needs of industry for flexibility as manufacturers strive to keep facilities fully operational with the goals of the agency to pursue regulations that require time intensive process or label changes?
    b. Will you ensure that the regulatory flexibilities and engagement to ensure the availability of safe and affordable food will continue?

**Response**: Should I be confirmed, I commit to take a close look at what steps FDA is taking during the pandemic to create flexibility for the food industry and will be committed to monitoring and mitigating any impact on food safety and food access for the American public. I'll also take a close look at any lessons learned that should inform how FDA looks at approaching the food supply chain in the future. Coming from North Carolina, a large agricultural state, I know how important it is that our food supply chains work and produce safe food to feed Americans.

15. Chlorpyrifos is a pesticide that does not have an effective, commercially viable alternative for many foods grown in the US. It has historically been used on over 80 crops— from row crops to fruit to vegetables nationwide. Despite Chlorpyrifos being a critical crop protection tool, on August 30, 2021, the EPA issued a final rule cancelling *all* food uses of Chlorpyrifos, starting February 28, 2022. This is despite recent court decisions (*see* Page 67) that did not tie EPA's hands to cancel the product for foods and also given the final rule contradicts EPA's own recent science on Chlorpyrifos that was published on December 3, 2020, in its Preliminary Interim Decision (PID) for Chlorpyrifos that rendered 11 continued uses of the product safe. Now, farmers are left scrambling not only to figure out an effective alternative and objecting to EPA's decision, but also in trying to determine how to manage 2021 crops treated with Chlorpyrifos in the supply chain. Many crops grown with the help of Chlorpyrifos in 2021 will be processed this year and into next year well past the February 28, 2022 tolerance revocation date. Needless to say, this is just one additional government-created supply chain issue our farmers could do without. EPA has stated for months it is "working" with FDA on guidance for 2021 Chlorpyrifos- treated crops in this situation for months. As such—
    a. Will EPA and FDA actually provide guidance? If so, on what exact date?
    b. In that guidance, will FDA state that such foods may be processed in the ordinary course by producers and/or third-party processors and any resulting food or feed products shall not be considered adulterated?
    c. Will EPA and FDA provide blanket guidance that commodities harvested in a lawful manner under FIFRA be legally processed and not be considered adulterated without the need for new record keeping requirements?

**Response:** I am aware of the action that EPA took, and the role EPA plays in the regulation of pesticides. This is a recent action that did not come up when I was last at FDA – but I commit to taking a close look at what steps FDA needs to take to respond to this EPA action and to facilitate decisions that farmers and food manufactures need to make. Coming from North Carolina, a state with a large agriculture industry, I know just how important it is that Federal agencies work closely with agricultural producers and state agriculture officials – and if confirmed, you'll have my commitment to do that.