

Questions for the Record
HELP Committee Hearing, November 17, 2015
“Hearing on the Nomination of Dr. Robert Califf to serve as FDA Commissioner”
Dr. Robert M. Califf

Senator Elizabeth Warren

1. Input of Pharmaceutical Industry Sponsors on Clinical Trials Conducted at Duke Clinical Research Institute

A. For the clinical trials you conducted or oversaw while at the Duke University School of Medicine and the Duke University Medical Center, can you detail for us exactly what input pharmaceutical sponsors did and did not have in the –

a. design of the trials?

Pharmaceutical (and device) sponsors provided input into the design of trials including the intervention, control measures, eligibility criteria, randomization, study endpoints, blinding methods, and sample size. In order for Duke to conduct the trial as the coordinating center, agreement must be reached by the academic leaders and the industry sponsor. All aspects of the design are included in the protocol, which is subject to review and approval by FDA, and for international trials, by regulatory authorities from each involved country and the European Medicines Agency. Finally, any participating research site has a Principal Investigator and an Institutional Review Board (IRB) that must review and approve the protocol in order to proceed with enrollment.

b. analysis of trial data?

Pharmaceutical sponsors provided input into the development of the statistical analysis plan. The plan is included in the protocol, which is subject to review and approval by FDA, by regulatory authorities in other countries, and the data monitoring committee (a committee of non-conflicted experts in the relevant medical specialty, clinical trial methodology, and ethics of human studies) Finally, as noted above, any participating research site has a Principal Investigator and an Institutional Review Board (IRB) that must review and approve the protocol with its included analysis plan in order to proceed with enrollment. The details of how the analyses are actually conducted are provided below.

c. publication of trial results?

After a publication was written by the academic investigators (including Duke investigators and other participating academic leaders), the pharmaceutical sponsor was given the opportunity to review and comment on the publication within a period of time that is specified in the contract. Final decisions about publication are made by the trial Executive Committee (which is comprised of the academic leaders). The industry sponsor has the right to review and comment, but no right to censor or dictate content or verbiage.

B. For each of the activities listed above

a. Which group had the final decision-making authority if differences arose between Duke academics and industry sponsors?

In situations in which the Duke academics were not in agreement with an industry sponsor regarding the design of a trial, the Duke academics did not participate in the trial. With regard to analysis of trial data and publication of trial results, the Duke academics always had the final decision-making authority per the terms in the contract regarding access to data and the right to publish. For example, the right to a copy of the database is what allows the academic group to perform an independent analysis and interpretation of the trial results.

b. Did industry sponsors have veto authority over decisions related to data analysis and the publication or presentation of trial results?

In trials coordinated by the DCRI, or in which I participated as a lead investigator, industry sponsors never had veto authority over decisions related to data analysis and the publication or presentation of trial results. As noted above, the majority of industry sponsored multi-site clinical trials do not have an independent academic coordinating center, so I believe the approach we developed at DCRI is best practice because it provides the independent voice in analysis and publication of results.

C. Referring to the input of pharmaceutical sponsors on the analysis of clinical trial data you said at the Senate HELP Committee hearing on November 17th: “Typically we’ll have an analysis done by the company and an analysis done by our statisticians, then we compare the results to see if they match up, and resolve any discrepancies. But in no case did we allow the company to do the analysis and we just were recipients of what they said the answer was.”

As a prelude to this series of questions, it is important to have some key background about industry-sponsored clinical trials:

- The majority of multi-site, industry-sponsored clinical trials do not have an academic coordinating center. They are coordinated by industry and for-profit contract research organizations. In cardiovascular medicine and many other highly evidence driven specialties, the independent role of the academic is an important element to ensure that the results are not biased, given the industry sponsor’s direct financial interest in the outcome. While most major academic medical centers have some coordinating center function, a limited number can conduct multi-national large trials, like the DCRI.
- The role of coordinating center is distinctly different from the role of a research site. The coordinating center assures that the trial is being conducted as designed by participating sites, collects the data from the sites, monitors the conduct of the trial, and does the analyses. The research site enrolls the patients, conducts the study protocol, and submits the data to the coordinating center. The research sites do not have a copy of the aggregate trial data and for the most part are not capable of doing the overall trial analysis.

a. Why might discrepancies between statistical analyses arise?

Databases from large, international clinical trials are complex with hundreds of thousands of pages of data and millions of data items. The analytical code to actually perform the analysis takes hundreds of hours to write and it is checked multiple times. There is also an audit trail to assure that analytical steps are not altered after unblinding. Because of this enormous complexity, there is great value in redundant checking both within the academic coordinating center and on the industry side and in checking between the two entities. All of this is done before unblinding the trial.

Academically coordinated trials that are not intended for regulatory review often do not have this level of rigor, which has led to concern about reproducibility. At the DCRI the procedures of checking and redundancy are standard for both industry-funded and government-funded trials.

b. How often did these discrepancies arise?

Because of the careful and extensive nature of this pre-unblinding work, it is very rare to have discrepancies that are significant, and, in fact, I'm not aware of any such instances. But small differences in coding and interpretation do occur, and it's critical to resolve these. Importantly, during this checking phase on the primary analysis, the statisticians are unblinded, but the clinical investigators and clinical development experts for the sponsor remain blinded.

c. Can you describe the process for "resolving discrepancies"?

When discrepancies arise in primary analyses, as described above, they are resolved prior to unblinding to eliminate bias. For secondary analyses and subsequent manuscripts, the academic coordinating center performs the analyses used for the study. These analyses typically are planned out in less detail prior to unblinding, but statistical analysis plans are constructed. Industry is welcome to provide a perspective from their own analyses, but control of the interpretation and message resides with the academic authors of the manuscript.

d. What factors are involved in making a final determination related to the analysis?

As stated above, the types of discrepancies encountered in the primary analysis are small and I have not encountered a situation in which a difference has occurred that would affect the interpretation of the trial.

e. Did Duke academics or the industry sponsor have the final decision over what analysis was submitted to the FDA?

Sponsors have the responsibility for regulatory submissions, which involve not only FDA, but the European Medicines Agency and dozens of national authorities for countries in which the product will be marketed. Accordingly, the sponsor has primary responsibility for the FDA submission, but the key analyses are duplicated by the academic coordinating center.

Was published by Duke academics?

Duke academics published in the context of the purview of the Executive Committee and the Steering Committee. The final decision was made by the Executive Committee of the trial. The sponsors, such as Johnson and Johnson and Bayer, had input into the primary manuscript, but no right to alter the decision of the Executive Committee.

Was published by the industry sponsor?

The industry sponsor is not charged with publishing key results of the trial independently of the academic coordinating center and Steering Committee. After the Steering Committee has published its primary manuscripts, the industry sponsor may make its data available for others to do analyses and publish the results.

D. How many publications have you authored or co-authored that report results from an industry-sponsored study regarding the safety or efficacy of that sponsor's product?

Please see question E below.

E. Please list publications you have authored or co-authored that report a negative result from an industry-sponsored study regarding the safety or efficacy of that sponsor's product.

The enclosed "Table A, Clinical Trials and Outcomes" contains a list of clinical trials in which I played a major role in the design, conduct, or oversight. The first column gives the acronym by which the trial was known.

The second column gives the publication reference. In cases in which I was an author, the manuscript is denoted by the number on my CV that was submitted to the Committee. Some trials are listed in which I played a major role, but was acknowledged in the list of Committees or in subsequent articles. In these cases the reference is given.

The third column gives the trial outcome:

- **Positive** means that the trial finding and interpretation favored benefit for the sponsor's product
- **Negative** means that the trial finding was not beneficial for the sponsor's product
- **Mixed** means that the finding was equivocal for the sponsor's product or more than one product was evaluated with mixed results
- **Non-inferior** means that the sponsor's product was found to be non-inferior to the comparator, and the trial was designed for this purpose. So, a non-inferior trial should be considered a positive finding from the sponsor's perspective.
- **Neutral** means that trial did not reach a conclusion about the product

Of the 55 trials in total, 28 (51 percent) were negative; 15 (27 percent) were positive; six (11 percent) were non-inferior; and six (11 percent) were either neutral (two) or mixed (four).

The fourth column identifies the medical product that was evaluated and the final column gives a brief summary of the finding.

As expected, the majority of trials did not show a positive outcome for the sponsor's product. From the perspective of an academic researcher, the desired outcome of a trial is that it answers an important clinical question (regardless of whether that finding was positive or negative). A review of all trials done by DCRI would have a similar distribution, reflecting the tremendous need for more trials to guide clinical practice. (See Table A. Clinical Trials and Outcomes).

[Submitted as a follow up: Table A, as submitted in response to the QFRs, is described as a 'list of clinical trials in which [Dr. Califf] played a major role in the design, conduct, or oversight,' but only contains trials that resulted in publications. Are there additional completed clinical trials in which Dr. Califf played a major role in the design, conduct, or oversight but which never resulted in publication? If so, what accounts for the lack of publications related to these trials?

I am not aware of any instance where the results of a clinical trial in which I played a major role in the design, conduct, or oversight were not published, so to the best of my knowledge, the list is complete.]

F. How does the conduct of privately funded clinical trials (wholly or in part) at Duke Clinical Research Institute differ from the conduct of clinical trials at other major medical centers in the United States?

To fully understand the response to this question, it is critical to know that clinical trials have 2 major organizational functions: the research site and the coordinating function. Most major academic medical centers and integrated health systems participate in hundreds of industry sponsored clinical trials as one of many research sites in each trial. As a research site, after agreeing that the study is meritorious and after independent review by the Institutional Review Board, the site conducts the trial and submits its data to a coordinating center. The individual research site is not equipped to analyze the trial data and does not have a copy of the aggregate data, nor should it, since the multi-site trials are needed to provide adequate sample sizes representative of the population likely to be treated with the therapy under evaluation, so that a single site analysis would not provide a valid scientific conclusion for the trial as a whole.

The coordinating center oversees the overall study organization, distributes and collects regulatory and operational documents and takes responsibility for overseeing the quality of the trial through a combination of auditing and monitoring the conduct of the trial and quality of the data. The coordinating center then does the analyses and manages the Steering Committee functions and interactions with the Data Monitoring Committee.

The Duke Clinical Research Institute (DCRI) is one of a small number of major academic medical centers in the United States with the capability of coordinating large global clinical trials. Most major medical centers participate in clinical trials in the role of a research site (i.e., enrolling patients at their institution in multi-site trials). So, DCRI performs many “coordinating center” functions which are not performed by most academic centers (such as clinical monitoring and safety surveillance). Coordinating center functions are also performed by commercial contract research organizations (CROs) which conduct this activity on a fee-for-service basis. Unlike academically-based coordinating centers, however, CROs do not have requirements for independent access to data and publication rights. A growing number of institutions have developed coordinating functions similar to DCRI for the same reasons, but few have the global reach or capacity of the DCRI.

G. Are the standards for preserving academic independence in sponsored research at Duke more stringent, less stringent or similar to standards at other peer institutions?

As noted above, an academic center may serve in the role of a coordinating center for a multi-site clinical trial or an individual research site responsible for enrolling patients at its institution in a multi-site trial.

The standards (i.e., contractual requirements) for preserving academic independence are different based on the institution’s role in the study. For example, since a specified sample size is required to discern whether a treatment is more or less safe and effective compared to another treatment (or to a placebo), the analysis of data from an individual research site is not scientifically valid. An individual research site would not typically require the right to publish the results of its own data, but rather would require that the aggregated data from all sites be subject to an independent analysis, interpretation and publication by the academic leadership of the trial.

Accordingly, an assessment of the stringency of the standards for preserving academic independence in the setting of a coordinating center requires comparison with those of other academic coordinating centers, rather than with those of individual research sites. Because Duke's standards for independent access to data and publication rights as a coordinating center are absolute, there is no situation in which its standards for preserving academic independence in sponsored research are less stringent than those of any peer institution.

2. Post-market Surveillance of Medical Devices

In response to a question from Senator Murray regarding post-market surveillance of medical devices during the Senate HELP Committee hearing on November 17th, you stated: "The Sentinel System.....is a model in drugs; we have 170 million Americans' claims data so when there is a problem with a drug we can look almost in real time. We need the same system on the device side." Unique Device Identifiers (UDI) will make post-market surveillance of devices possible, but only if they are captured in electronic health information.

A. What steps need to occur before the FDA can integrate UDIs and medical device information into the Sentinel System, as mandated by Congress in the 2012 Food and Drug Administration Safety and Innovation Act?

FDA, the Office of the National Coordinator for Health IT (ONC), and the Centers for Medicare & Medicaid Services (CMS) are working closely on the shared goal of incorporating UDIs into electronic health records (EHRs), starting with implantable devices. The recently finalized rules on the 2015 HIT Certification Criteria (ONC) and

Medicare and Medicaid Electronic Health Record Incentive Programs—Stage 3 and Modifications to Meaningful Use in 2015 Through 2017 are important steps in this process as both support the addition of UDIs for implantable medical devices to the Common Clinical Data Set which would be able to be exchanged and available to providers who care for the patient.

In addition, FDA and CMS look forward to continuing to explore options that would improve surveillance in a timely and effective manner. These agencies are committed to capturing appropriate data and sharing information transparently to improve the quality and safety of care delivered to people across the nation. FDA and CMS also support the recommendation by the National Committee on Vital and Health Statistics to consider conducting voluntary pilot tests of the benefits, costs, and feasibility of UDIs in claims reporting between providers and commercial payers.

Voluntary pilots should address key challenges to adding UDIs to claims, including significant technological hurdles and costs (for providers, payers and others), as well as difficulties in validating UDIs reported on claims.

B. As a cardiologist and clinical trials expert who has experience with real-world data sources, how do you understand that UDI information in medical claims could support the evaluation of medical devices after approval—such as through enhancements to registries like those operated by the American College of Cardiology and to expand the Sentinel system?

The current Sentinel data model focuses on querying administrative and claims data maintained by partner organizations who share aggregated results with FDA. FDA does not receive or hold personally

identifiable information, but can query privacy-protected data and receive aggregated data from local environments that together cover approximately 126 million patients.

These records generally lack manufacturer or brand-specific device identifiers and therefore cannot be leveraged to perform meaningful medical device post-market surveillance. While CDRH is actively engaged in promoting the integration of UDI into electronic health information, we are also undertaking complementary efforts to develop a more comprehensive evaluation system for medical devices. FDA is exploring the means to expand Sentinel by linking national device registries to these claims data. We are currently linking clinical registries to claims data to enable the evaluation of longitudinal data. Clinical registries collect information that uniquely identifies and provides curated clinical data in selected medical device areas. These activities, along with establishing linkages to electronic health records, are envisioned to be the building blocks of a broader National System for Medical Device Post-market Surveillance [<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm>] that would use evidence from clinical experience in a network of existing electronic data systems to improve patient safety, enhance our understanding of device performance, and facilitate device innovation.

C. If UDI information is not included in claims data, what negative repercussions would that have for the Sentinel system to evaluate specific medical devices?

The current Sentinel data model focuses on querying administrative and claims data maintained by partner organizations, who share aggregated results with the FDA. FDA does not receive or hold personally identifiable information, but can query privacy-protected data and receive aggregated data from local environments that together cover approximately 126 million patients. These records generally lack manufacturer or brand-specific device identifiers.

D. What are the benefits of the integration of UDIs into electronic health records?

UDIs incorporated into electronic health information, especially electronic health records and medical device registries, can help create additional, more robust, and cost-effective post-market monitoring and surveillance data sources and support additional device research by leveraging real world clinical data. UDIs allow us to more easily link the use of a device with a patient's experience with that device.

UDIs incorporated into electronic health information will also help the FDA, the health care community, and industry to:

- More accurately report and analyze device-related adverse events by ensuring that devices associated with these events are correctly identified.
- More rapidly develop solutions to reported problems.
- More efficiently resolve device recalls, including the removal of potentially harmful devices from the market.
- Reduce medical errors by enabling health care professionals and others to rapidly and precisely identify a device, obtain important information concerning the device's characteristics, and improve the identification of the device through the distribution chain to the point of patient use.

The Unique Device Identifier (UDI) system is essential to transforming postmarket surveillance of medical devices; a critical cornerstone of FDA's strategy is the incorporation of UDIs into electronic health information, particularly electronic health records (EHRs) and device registries. In the 2012 Food

and Drug Administration Safety and Improvement Act, Congress required FDA to expand Sentinel to include medical devices.

E. How do you plan to work with the Centers for Medicare and Medicaid Services, the Office of the National Health Coordinator for Health Information Technology, private payers, and the medical device industry to facilitate the integration of UDIs into multiple sources of electronic health information?

FDA, the Office of the National Coordinator for Health IT (ONC), and the Centers for Medicare & Medicaid Services (CMS) are working closely on the shared goal of incorporating UDIs into EHRs, starting with implantable devices. The recently finalized rules on the HIT Certification Criteria (ONC) and Medicare and Medicaid Electronic Health Record Incentive Programs—Stage 3 and Modifications to Meaningful Use in 2015 Through 2017 are important steps in this process as both support the addition of UDIs for implantable medical devices to the Common Clinical Data Set which would be able to be exchanged and available to providers who care for the patient.

3. Antibiotic Resistance – Antibiotic Use in Animal Agriculture.

While FDA policies (Guidance for Industry (GFI)#209 and #213 and the Veterinary Feed Directive Final Rule) make the use of antibiotics to promote animal growth illegal and subject all remaining uses of antibiotics to veterinary oversight, I remain very concerned that these policies leave the door open for dangerous antibiotic regimens to continue. FDA officials have previously communicated to me that they plan to monitor the removal of growth promotion from labels.¹ However, measuring how many companies make promised changes in their drug labels is not an adequate measure of whether the policies have been successful at ending the misuse and over-use of antibiotics in animal agriculture.

Additionally, FDA’s policies will work only if veterinarians follow appropriate prescribing guidelines that take into account not only the health of the animals in front of them, but also consider the public health. GFI #213 describes principles that veterinarians should consider when determining the appropriateness of antibiotic use for disease prevention. FDA has stated that the agency “intends to work with veterinary and animal producer organizations to reinforce the importance of these principles.”² However, representatives from many animal producer organizations have publically voiced doubts about the need to reduce antibiotic use and the impact that the FDA’s policies will have on the amount of drugs used.³

A. Given documented disagreements among stakeholders, and given that veterinary adherence to appropriate antibiotic prescribing guidelines is a critical part of FDA’s policies, how will you, as Commissioner, monitor, evaluate, and take necessary actions with regard to compliance with GFI #213’s appropriate antibiotic prescribing guidelines?

The Food and Drug Administration (FDA or the Agency) is confident that the changes under its judicious use policy, as outlined in Guidance for Industry (GFI) #209 and GFI #213, will be effectively

¹ Secretaries Burwell, Carter, and Vilsack to Senator Warren, Aug. 17, 2015.

² Kraus, Thomas A., Associate Commissioner for Legislation, FDA to Senators Warren, Feinstein and Gillibrand, Sept. 8, 2014; FDA, *Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*. December, 2013. (pg.7)

³ Christine Hoang, American Veterinary Medical Association (AVMA), on “The Trouble with Antibiotics,” PBS Frontline, October 2014; AVMA Antimicrobial Use and Antimicrobial Resistance FAQ; Ron Philips, Animal Health Institute, in Flynn, Dan (27 May 2011) “Ag Coalition Says Antibiotic Facts are on Its Side.” *Food Safety News*; Coalition letter to David Hoffman, PBS Frontline Producer, August 2014; Juan Ramon Alaix, Zoetis in Loftus, Peter. (2013 Nov. 19). Zoetis Chief Leads Animal-Health Firm Following Split from Pfizer. *The Wall Street Journal*.

implemented. FDA has received written commitments from all affected pharmaceutical companies to align their products with the GFI #213 recommendations. There has been positive engagement of key stakeholders, including the animal pharmaceutical industry, the animal feed industry, and veterinary and animal producer organizations. Furthermore, once the affected products are aligned, it will be illegal to use these medically important antibiotics for production purposes or to use these products for the remaining therapeutic purposes without the authorization of a licensed veterinarian. Veterinarians play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, and prevent disease.

The President's National Action Plan calls on FDA to collaborate with veterinary organizations, animal producer organizations, the animal feed industry, and others to develop and implement educational outreach efforts to ensure that veterinarians and animal producers receive the necessary information and training to support implementation of GFI #213. As part of these efforts, FDA is working with the U.S. Department of Agriculture (USDA) to ensure that veterinarians have access to timely, updated information and training for the appropriate use of medically important antibiotics in the feed and water of food-producing animals. For example, FDA is developing guidance on the Veterinary Feed Directive (VFD) form, which veterinarians will use, as well as supporting changes to veterinary curricula, and leveraging many opportunities to provide necessary education via our partnerships with various stakeholders.

As part of its compliance efforts, FDA will utilize its authority to conduct inspections that will provide important information for determining compliance with GFI #213. For example, VFD records will be examined as part of inspections conducted at feed manufacturing facilities. Examination of such records is an important tool for determining whether these drugs are being appropriately authorized. In addition, as part of the recent revisions to the VFD regulation, FDA updated requirements for the establishment (by veterinarians) of a veterinary-client-patient relationship (VCPR) when a veterinarian authorizes the use of a VFD drug. Since veterinarians are licensed at the state level, FDA is working closely with the state boards of veterinary medicine on this issue.

Ongoing surveillance of antibiotic use and resistance is also a critical element of FDA's strategy for assessing the impact of FDA's GFI #213. FDA's data collection efforts include enhancements to the collection and reporting of data collected under the National Antimicrobial Resistance Monitoring System (NARMS), enhancements to the collection and reporting of antimicrobial sales and distribution data, as well as ongoing collaboration with USDA to collect additional on-farm data on antibiotic use and resistance. FDA co-sponsored a public meeting with USDA and the Centers for Disease Control and Prevention (CDC) on September 30, 2015, to obtain input from the public on approaches for enhancing collection of data on antibiotic use and resistance in animal agricultural settings. These efforts will allow FDA to better assess the effects of antibiotic stewardship policies and analyze the association between antibiotic use and resistance.

The efforts that are currently underway represent a significant step forward in addressing antimicrobial resistance. We acknowledge that this is an ongoing effort and additional measures may be needed. In addition to effectively eliminating growth promotion use and instituting veterinary oversight, we recognize the importance of ensuring that meaningful stewardship principles are applied in conjunction with the use of medically important antimicrobial drugs for therapeutic purposes, including for disease prevention. FDA is committed to working in collaboration with USDA, CDC, veterinarians, animal producers, and other stakeholders on this important effort.

B. As Commissioner, what currently available data sources will you use to measure the success of FDA's current antibiotic use in animal agriculture policies at addressing the overall public health threat?

C. How will you work with USDA to prioritize the development of additional data sources, including measures of how antibiotics are used on farms?

Gathering information on the way medically important antibiotics are used is essential to assessing the impact of FDA's judicious use strategy. FDA has several data sources currently available to measure antibiotic use in animal agriculture.

Under section 105 of the 2008 Animal Drug User Fee Amendments (ADUFA 105), drug sponsors must report to FDA annually on all antimicrobials sold or distributed for use in food-producing animals. FDA collects, summarizes and reports this information annually in its ADUFA 105 report. In 2014, FDA enhanced the format of its annual summary report so that it now includes information on the importance of the drug in human medicine and provides aggregate data on the approved route of administration of antimicrobial drugs sold or distributed for use in food-producing animals, whether such drugs are available over-the-counter or require veterinary oversight, and whether they are approved for therapeutic indications, or both therapeutic and production indications. FDA also reanalyzed previous years' reports in the same manner. In May 2015, FDA proposed revisions to the ADUFA 105 reporting requirements in order to obtain estimates of sales by major food-producing species (cattle, swine, chickens, and turkeys). The additional data would help FDA further target its efforts to ensure judicious use of medically important antimicrobials. The public comment period closed on August 18, 2015, with varying reactions from stakeholder groups. The final rule is an FDA priority, and we hope to publish it next May.

In addition, FDA collaborates with USDA and CDC to collect data on antimicrobial resistance among foodborne pathogens as part of NARMS. Recent enhancements to the NARMS program make the data more useful for measuring the effects of GFI #213, particularly a new USDA Food Safety Inspection Service slaughter-sampling program, launched in March 2013, which increases national representativeness of the animal samples. FDA is also working with state partners to perform whole-genome sequencing on NARMS samples, which will provide unprecedented details on the traits of resistant strains of foodborne bacteria from animals and animal-derived foods. In August 2015, FDA released its 2012-2013 NARMS Integrated Report, which overall reveals mostly encouraging findings, with some areas of concern.

On September 30, 2015, FDA, in collaboration with USDA and CDC, held a jointly-sponsored public meeting to obtain public input on possible approaches for collecting additional on-farm antimicrobial drug use and resistance data. Information from the public meeting will help FDA determine the most efficient way to collect the additional on-farm use data needed to assess GFI #213's impact on antimicrobial resistance. Combined with existing sales data on antibiotic drugs sold for use in food-producing animals and the data from NARMS, the new on-farm data will provide a more comprehensive and science-based picture of antibiotic drug use and resistance in animal agriculture. This data collection plan is intended to provide the data needed to: a) assess the rate of adoption of changes outlined in the FDA's GFI #213, b) help gauge the success of antibiotic stewardship efforts and guide their continued evolution and optimization, and c) assess associations between antibiotic use practices and resistance trends over time.

In addition, FDA and USDA are collaborating with a Cornell University researcher through the National Institute of Mathematical and Biological Synthesis (NIMBioS) to develop a new mathematical modeling methodology that would inform the approach to monitoring and assessing the impacts of GFI #213. The

work of this group is still ongoing. The working group has so far met in September 2014 and February 2015 (meeting summaries are available at http://www.nimbios.org/workinggroups/WG_amr).

D. What result or results – based on those data sources – would indicate to you that the policies have been successful or unsuccessful?

FDA believes it is important to assess progress in the context of five key components or phases of the overall effort. First, FDA focused on engaging the animal pharmaceutical industry and the animal agriculture community more broadly to work cooperatively with FDA to implement the changes outlined in FDA’s judicious use strategy. FDA has been able to successfully gain commitments from all affected drug companies.

Second, FDA is focused on working with these affected drug companies to complete the transition from old labeling to new labeling, to remove all growth promotion indications, and bring the remaining therapeutic indications for these products under veterinary oversight. FDA is currently in the middle of the three-year implementation period for implementing these label changes by the target date (end of December 2016). FDA expects all affected products to be aligned by this target date.

Third, FDA continues to engage consumer advocacy groups to ensure transparency of our efforts and that the appropriate public health risks related to antimicrobial use in food producing animals are identified and addressed.

Fourth, FDA is currently working with USDA and CDC to develop approaches for collecting additional on-farm data on antibiotic use. Having better data on actual antibiotic use practices at the farm level will enhance our ability to assess whether our policies are having the desired effect to align such antibiotic use practices with good stewardship/judicious use principles.

Finally, FDA is also working with USDA and CDC to develop approaches for collecting additional on-farm data on antibiotic resistance. This additional information, along with other sources of resistance information such as that provided by NARMS, will better enable us to assess whether our policies are having the desired effect to reduce resistance.

The additional data collection efforts described above will all play an important role in assessing the impact of current as well as future measures that are implemented to address this important public health issue.

4. MSM

Earlier this year, the FDA released the “Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products: Draft Guidance for Industry” which, if finalized, would change the blood donation policy for men who have sex with men (MSM) from a lifetime deferral to a one-year deferral from last sexual contact with another man. I am pleased that the FDA has finally taken this first step towards lifting the lifetime deferral. However, the one-year deferral policy is still not based on science, not based on an individual donor’s risk of carrying a transfusion transmissible infection, still prevents many low-risk individuals from donating blood, continues to let higher risk individuals donate, and gives no signal that the FDA that the agency is committed achieving a fully risk-based system for all donors. If you are confirmed Commissioner –

A. Are you committed to ending the lifetime deferral policy for MSM?

The Food and Drug Administration (FDA) takes its responsibility to regulate the blood supply and to ensure its continued safety for patients who receive potentially lifesaving blood products very seriously, and also understands the need to update these policies to reflect current science. In collaboration with other government agencies, and considering input from advisory committees, the FDA has carefully examined the available scientific evidence relevant to the blood donor deferral policy for men who have sex with men (MSM) and recommended a change in the blood donor deferral period for MSM from indefinite deferral to twelve months since the last sexual contact with another man. We intend to issue final guidance in the near future. In addition, FDA is committed to continuing to work with stakeholders to develop the most optimal deferral strategies, including investigating individual risk assessment.

B. When the Draft Guidance is finalized, how do you plan to reach out to the MSM community to explain the change in the lifetime deferral policy and encourage these individuals to donate?

FDA intends to reach out to stakeholders, including the LGBT community as part of the rollout for the final guidance, when it publishes. We will explain the changes to the policy and answer any questions regarding blood donation.

C. What is your plan to ensure that the one year deferral policy is only a first step toward implementing a risk-based blood donation policy for all blood donors, including MSM?

FDA has examined the available scientific evidence relevant to the blood donor deferral policy for men who have sex with men (MSM) and recommended a change in the blood donor deferral period for MSM from indefinite deferral to twelve months since the last sexual contact with another man. We intend to issue final guidance in the near future. In addition, FDA is committed to continuing to work with stakeholders to develop the most optimal deferral strategies, including investigating individual risk assessment.

FDA has already taken steps to implement a national blood surveillance system that will help the agency monitor the effect of a policy change and further help ensure the continued safety of the blood supply and to develop scientific evidence potentially relevant to making further changes to the blood donor deferral policy in the future.

Implementation of the surveillance system is not contingent upon changing FDA's blood donor deferral policy for men who have sex with men. The system will monitor a majority of the blood collected in the United States for a number of different transfusion-transmitted viral infections, including HIV. We anticipate that the system will provide important information that will be helpful as we continue our efforts to further enhance the high level of safety of the U.S. blood supply and potentially support further revisions to our blood donor deferral policies.

5. Clinical Trial Data Sharing

A study entitled "Clinical trial registration, reporting, publication and FDAAA compliance: a cross-sectional analysis and ranking of new drugs approved by the FDA in 2012," published last week in the British Medical Journal, found that several major drug companies have not met the standards for clinical trial results reporting under the Food and Drug Administration Amendments Act (FDAAA) of 2007. FDAAA established civil monetary penalties of up to \$10,000 per day for non-compliance, and yet the FDA has never been imposed.

A. What do you do you believe the impact of greater transparency of clinical trial data and results would be on –

- a. Clinical trial efficiency**
- b. The cost of drug development**
- c. Drug safety**
- d. Biomedical innovation**

FDA supports the view that transparency of clinical trial data and results is in the public interest. FDA is committed to increasing the transparency of information available regarding clinical trials and supports the principle of providing increased access to registration information and clinical trial data and results. The requirements in Title VIII of FDAAA have resulted in greater access to information for significant numbers of clinical trials. The public, and particularly clinical trial participants, benefit from access to these results. An additional benefit of the transparency provided by ClinicalTrials.gov is that it may provide FDA reviewers with a fuller picture of the trials under way in a particular area. Such information could contribute to current efforts to improve the design and quality of clinical trials and provide additional analytical tools and methodologies for analyzing clinical trial data and results.

FDA's role in protecting and helping to ensure the safety and efficacy of medical products, however, does not depend on data reported to the ClinicalTrials.gov databank. FDA's regulatory and surveillance mechanisms for identifying potential medical product problems and alerting patients and health care professionals are broad and continue to improve through programs such as the Sentinel Initiative. Dissemination of research results is a fundamental and long-standing principle of science and affords clinical trial participants the opportunity to know the value of their participation. Such access informs future research and can improve study design as well as prevent duplication of unsafe trials. Ultimately, greater transparency of clinical trials results will enhance public trust in clinical research. The additional impacts on safety as a result of this transparency and any effects such transparency may have on the costs of drug development.

B. If you are confirmed Commissioner –

- a. How do you plan to work with the NIH to finalize the Proposed Rule issued this spring to fully implement and clarify the FDAAA policy?**
- b. How will you ensure compliance to the disclosure policy implemented by FDAAA?**
- c. Will you enforce the law using civil monetary penalties or by other means?**

FDA worked with NIH to issue the Proposed Rule (published in November 2014) and continues to work with NIH to develop a final rule to implement the FDAAA requirements. The comments made to the Proposed Rule were complex and raised a number of issues that FDA is reviewing carefully and cooperatively with NIH. Although NIH is the lead for developing and finalizing the regulations and for implementing the ClinicalTrials.gov databank, FDA has the responsibility for enforcing the FDAAA ClinicalTrials.gov requirements. However, enforcement actions are not the only tools used by FDA to ensure compliance with the statutory requirements. FDA has undertaken significant compliance efforts with regard to the ClinicalTrials.gov requirements, even in the absence of a final rulemaking, and will continue to do so even after a final rule is effective. However, without a final rule explaining the statute's requirements, thus putting all affected parties on a level playing field, a full enforcement program cannot be implemented. When NIH finalizes the rule, FDA will be in a better position to increase its compliance/ enforcement actions. The use of civil money penalties

will depend on each case and the applicability and appropriateness of seeking such penalties. It will be part of the enforcement “tool set.”

6. Patient Medication Information

While the FDA strictly regulates the prescribing information meant for doctors and requires the Drug Facts on over the counter medications, patient information about a medication and its potential risks is largely unregulated. The FDA has been working in collaboration with the Brookings Engelberg Center for Health Care Reform since May 2010 to engage in research and facilitate discussions among stakeholders regarding the design, implementation, and evaluation of a PMI document. Janet Woodcock testified before the Senate Aging Committee in December 2013 to discuss the FDA's ongoing work to develop consumer-friendly patient medication information (PMI) documents. I sent a letter asking about the FDA's timeline for implementation with Senators Gillibrand, Nelson, and Blumenthal in March 2014, but received no information in the agency's response. As Commissioner, are you committed to issuing regulations that will require consumer-friendly patient medication information to be provided with prescription medications before the end of this administration?

FDA is in the process of developing proposed rulemaking for PMI and regulations of this type require significant public input, consumer research, and economic analysis. In order to obtain information to determine the best path forward for patient medication information, FDA has conducted research and continues to engage with interested stakeholders including patients, industry, and others, on how to improve the content and availability of PMI. These meetings have included an open public hearing on PMI in September of 2010, as well as four public workshops with the Engelberg Center for Health Care Reform at the Brookings Institution since 2010 that discussed optimizing, implementing, and evaluating the adoption of PMI, the last of which was held on July 1, 2014. In addition, RTI published the results from the qualitative portion of FDA's PMI study (75 FR 78252) on October 14, 2014, in an article entitled, “Preferences for Patient Medication Information: What Do Patients Want?”

FDA is in the process of developing proposed standards for PMI format and content, a central repository to serve as a source for PMI, and methods of distribution to patients and pharmacies.

FDA continues to be committed to the development of a PMI framework where the focus is on patient comprehension and issuing regulations in a timely manner.

7. Biosimilars

The Affordable Care Act established a pathway for the approval of biosimilar drugs that will create competition in the biologic drug market. Over five years since this pathway became law, FDA has still not established clear rules of the road for drug makers, and many key guidance's, including those on naming, labeling, and interchangeability have not been finalized. If you are confirmed Commissioner

A. What timeline will you implement for finalizing the outstanding guidance's?

FDA has published the following final guidances related to biosimilars: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product; Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product; and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009; and Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants.

FDA has also published the following draft guidances since 2012: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act; Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009; and Nonproprietary Naming for Biological Products.

The Agency is committed to carefully reviewing the comments received as we move forward in finalizing the draft guidances noted above. Upcoming guidances are expected to include: Considerations in Demonstrating Interchangeability to a Reference Product; Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity; and Labeling for Biosimilar Biological Products.

FDA is diligently working to issue guidance on issues that have been identified by the FDA and key stakeholders as key topics of interest. While the Agency cannot provide a specific timeline for the release of any guidance, we continue to provide information to assist biological product developers - sponsors/companies - with bringing biosimilar and interchangeable products to market. The FDA is continuing to clarify its approach to implementation of the BPCI Act to further facilitate sponsors' development of biosimilars and interchangeable biological products.

B. How do you plan to work with the medical and patient community to educate them about biosimilars to avoid inaccurate perceptions – like those that are still prevalent about generic drugs over 30 years since Hatch-Waxman?

FDA has a multi-phase plan for communicating with stakeholders about biosimilars. The first phase of communication is to lay a solid foundation with basic definitions and descriptions about biosimilars that health care professionals and consumers can easily understand and adopt. Concurrent with the approval of Zarxio, the first biosimilar licensed in the United States, FDA used a number of tools to help reach the medical and patient community, including working with stakeholder groups, including professional associations, to share the details on the new approval and encouraging them to disseminate to their memberships; updating the consumer tools on our web site, including development of a user-friendly consumer update, and providing Web content that includes background information such as definitions of biosimilar products and interchangeable products, information on how these products are prescribed, and the differences between biosimilar products and generic drugs. FDA plans to communicate information in various formats to consumers as more biosimilar products are licensed and enter the marketplace, and as FDA issues additional guidance on topics such as labeling, naming, and interchangeability. In addition to developing communication materials, as part of its multi-phase plan, FDA is conducting research on prescriber's knowledge and perceptions of biosimilars. This research will help inform future outreach and education efforts to both health care professionals and consumers. Moving forward, FDA will continue to implement other phases of its biosimilars communication plan to increase health care provider and consumer confidence in this new category of products.

C. How do you plan to work with CMS and private insurers to help inform their biosimilar policies to be sure that they are consistent with science, encourage market competition, and encourage innovation?

While the FDA does not have a role in coverage and payment decisions by CMS or other insurers, however, FDA and CMS regularly communicate about pharmacovigilance.

FDA recognizes that healthcare providers have consistently indicated the importance of assurance that biosimilars will not have clinically meaningful differences from the originator, or reference product. FDA applies a scientifically rigorous review process and approval standard to earn and sustain confidence in biosimilar products and interchangeable products. We are committed to providing this assurance and recognize its importance to the acceptance of these products, and the future success of the biosimilars program.

8. Opioids

America is in the midst of an opioid epidemic. According to the Substance Abuse and Mental Health Services Administration, 4.3 million Americans reported use of prescription painkillers for non-medical reasons in the last month, and according to the Centers for Disease Control, 16 million Americans died of an opioid overdose in 2013. Congress has signaled an especially vested interest in reduce the impact opioids on pregnant women by passing the Protecting Our Infants Act of 2015, championed by my colleague from Massachusetts, Representative Katherine Clark.

A. What role do you believe the FDA has in combating this epidemic?

Misuse, abuse, addiction, and overdose of opioid medications have become a public health crisis in this country. FDA plays an important role in helping to address this issue. Our work supporting the development of non-opioid pain medications, the development of abuse-deterrent formulations of opioid drugs (including generics), and improving prescriber education are Agency priorities.

I am committed to doing what we can to curb the abuse of these drugs. We also understand the need to balance efforts to address the abuse and misuse of prescription opioid medications with legitimate and safe use of pain medicines by patients who need them.

Our hope is that there will be alternative treatment options for pain management using non-opioid pain medications. We are actively encouraging and supporting the development of such products.

At the same time, FDA will continue to work to reduce the risks of opioid abuse and misuse, but we cannot solve this complex problem alone. A comprehensive and coordinated approach is needed; one that includes federal, state and local governments, public health experts, health care professionals, addiction experts, researchers, industry, and patient organizations.

B. If you are confirmed as Commissioner, what FDA authorities could you use to help address the opioid crisis?

FDA will act within its authorities, based on science, to address the opioid crisis. When appropriate, the Agency is using its expedited programs to speed the development of products like non-opioid pain medications, abuse-deterrent formulations and formulations of naloxone that are easier to use.

Also, FDA can require a risk evaluation and mitigation strategy (REMS) when necessary to ensure that the benefits of a drug outweigh the risks. In 2012, using this authority, FDA required manufacturers to make available continuing education programs on opioid prescribing practices for prescribers. Under the REMS for extended-release/long-acting (ER/LA) opioid analgesics, manufacturers have also developed a patient-friendly counseling tool for prescribers to give to every patient, when they write a prescription for an ER/LA opioid. The REMS also includes a product-specific Medication Guide to be provided to the patient when they pick up their prescriptions. Included in these materials is information on how to

safely store medications, while still in use, and what to do with the leftover supply, when it is no longer needed. We are in the process of evaluating the effectiveness of the ER/LA opioid analgesics REMS and whether any changes are appropriate.

Additionally, FDA held a public meeting and opened a public docket in February 2013 to hear from researchers, patients, health providers about issues concerning opioids, including the approved labeling for opioid medications and how it is used in clinical practice.

We listened and reviewed the science. As a result, FDA required important changes to the labeling of all ER/LA opioid analgesics. In April 2014, we finalized these required changes to the labeling for these drugs, changing their indication to inform prescribers that these drugs should only be used for pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate to provide sufficient pain relief. At the same time FDA significantly strengthened the safety warnings for these opioids. We want prescribers to use these medicines with care, and today the labeling for ER/LA opioid medicines have some of the most serious warning language that can be found in drug labeling, including a boxed warning about their potential for abuse, and clear language that calls attention to their potentially life-threatening risks.

There are additional existing post-marketing requirements for all of the ER/LA opioid analgesics that include a requirement to conduct one or more studies to provide quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics for management of chronic pain, among patients prescribed ER/LA opioid products.⁴ We are working with sponsors to develop this information and these studies are currently underway.

C. How do you plan to expand our knowledge base about the safety of all drugs in pregnant and lactating women?

Understanding that adequate information on the use of medications in pregnant and lactating women is extremely sparse, the Agency supports efforts to spur greater research and development in these patient populations. Such efforts must focus on building a greater foundation for both the quality and quantity of research, such as basic pharmacokinetic data, as well as addressing key policy issues that hinder additional research on the use of drugs in pregnant and lactating women.

Of note, the Agency intends to publish two revised guidances to reflect the Agency's current thinking regarding expert/scientific opinions and to ethical issues surrounding clinical evaluation of drugs used in pregnancy and lactation. These revised policy documents, *DRAFT Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis & Recommendations for Labeling*, and *DRAFT Guidance for Industry: Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling* are in the final stages of the drafting process. In addition, following the May 2014 Pregnancy Registry Public workshop, the Agency has been engaged in revision of the *Guidance for Industry: Establishing Pregnancy Exposure Registries* to reflect key conclusions from this public meeting.

The Agency is also focused on improving communication of known information on the use of prescription drug and biological products in pregnant and lactating women in the labeling of these products. On December 4, 2014, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling*” rule, also known as the

⁴ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm>

Pregnancy and Lactation Labeling Rule (PLLR), was published in the Federal Register.⁵ The rule went into effect on June 30, 2015. The rule amends the Physician Labeling Rule⁶ requirements for how information is presented in the pregnancy and lactation subsections of labeling for prescription drugs and biological products. The rule replaces the product letter categories—A, B, C, D and X—used to classify the risks of using prescription drugs during pregnancy with a description of risks within the real-world context of caring for pregnant women who may need prescription drug and/or biological products. These changes in product labeling will help ensure labels more effectively communicate important health information where prescribing decisions during pregnancy and lactation are generally individualized and involve complex maternal, fetal and infant risk-benefit considerations. The PLLR content and formatting requirements provide a more consistent way to include relevant information about the risks and benefits of prescription drugs and biological products used during pregnancy and lactation based on available information.

There is a major need to invest in clinical research in pregnant women. The success of treatment of congenital and childhood diseases has dramatically increased the need for pharmacologic treatment of chronic diseases during pregnancy. Yet, we have only a fraction of the information that we have obtained in children, because very few studies have been done. Recent FDA rules have improved the labeling of drugs for pregnant women because the old pregnancy letter category system was overly simplistic and often misleading. The new format is structured to more clearly describe available data that can be used to aid in complex risk/benefit discussions between prescribers and their patients. However, in many cases there is still a lack of high-quality data to inform about the risks of a drug when used during pregnancy. In such cases, the new labeling format also includes required statements to communicate that data are lacking.

⁵ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁶ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the *Federal Register* (71 FR 3922; January 24, 2006).