Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" FDA User Fee Reauthorization: Ensuring Safe and Effective Drugs and Biologics "
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The Honorable Michael C. Burgess, M.D. (R-TX)

Response: Thank you for these thoughtful questions regarding the use of real-world evidence (RWE) in the regulatory review process. Please find my responses below to the questions posed. I would also be happy to meet to discuss the questions and responses further.

1. **According to your testimony you seem to imply that there is an intent to replace clinical trials with real-world evidence (RWE). To my knowledge, RWE has been used very successfully to supplement data from clinical trials, and the goals in PDUFA VII are aimed at trying to improve how we can use RWE and to evaluate the potential for new use cases. Is that not the case?**

   Real-world evidence (RWE), which is defined by the FDA as "information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing date, product and disease registries, and data gathered through personal devices and health applications", has helped inform regulatory decision-making, complementing robust clinical trials.[1] For instance, RWE has been utilized in capturing safety signals for new drugs and medical devices that would not have otherwise been captured until these products were made available in clinical practice to a larger population of patients and for a longer duration than that of clinical trials. FDA's Sentinel Initiative is an example of such a platform that harnesses and harmonizes real-world data (RWD) through EHRs, claims, and other data sources from insurers and healthcare delivery systems.[2]

   Moreover, RWE has been used to inform supplemental indication approvals for medical products already on the market. For instance, FDA approved additional indications for transcatheter heart valves with evidentiary support form data collected in a postmarket valve registry that was created as a result of a Medicare coverage decision.[3] Just last year, FDA for the very first time utilized real-world evidence to approve Prograf (tacrolimus) in combination with other immunosuppressant medications for the supplemental indication of preventing organ rejection in adult and pediatric patients receiving lung transplantation.[4] For this approval, FDA used robust RWD sources including U.S. Scientific Registry of Transplant Recipients (SRTR), which has data collected on all lung transplants in the country. This was further augmented by a trusted data source on

mortality from the Social Security Administration's Death Master File. FDA worked closely with the manufacturer to design a rigorous, non-interventional trial to demonstrate a significant improvement in outcomes among lung transplant patients who received Prograf as part of the immunosuppressant regimen compared to those who did not. It should be noted that FDA also considered randomized-controlled trials of the drug in other solid organ transplant patients as confirmatory evidence as well as other published clinical trial evidence.

While there is growing evidence of the potential capability of RWE to be used complementary to clinical trials in the regulatory review process, proposals have emerged to more hastily allow for RWE to replace clinical trials, particularly for supplemental indications and fulfillment of postapproval study requirements. Such proposals include:

- H.R. 6996, the *Accelerating Access for Patients Act* would allow for sponsor to utilize "clinical evidence, patient registries, or other sources of real-world evidence" to fulfill postapproval study requirements (Sec(2)(a)(2)(A)). The legislation also asks FDA to issue a report within 180 days of passage around the current use of RWE in supporting or fulfilling postapproval confirmatory study requirements (Sec(2)(a)(6)(A) and (B)).[5]
- H.R. 6000, *Cures 2.0* would allow RWE to be submitted as confirmatory evidence of clinical benefit to fulfill postapproval study requirements (Title III – Section 309).[6]
- Within FDA's PDUFA VII Commitment Letter,[7] FDA committed to establishing a pilot "Advancing RWE Program" that would identify approaches for generating RWE in "support of labeling for effectiveness or for meeting postapproval study requirements." Under this program, FDA will solicit sponsors through a competitive application process to pilot RWE approaches that can feasibly be used as part of the regulatory review process. Such an approach does have the potential in providing FDA with further information on the advantages and limitations of RWE in making regulatory review decisions, including for new indications and fulfillment of postapproval studies meant to confirm clinical benefit. This could enable necessary improvements to RWD sources in a stepwise manner unlike the aforementioned legislative proposals that would pre-empt such improvements from being made to RWD sources.

My colleagues examined whether it would be feasible to use such RWD sources in the form of EHR or claims data to emulate FDA-required postapproval confirmatory trials for all new drugs that received accelerated approval between 2009 and 2018.[8] Of the 50 confirmatory trials required by the FDA for these drugs, none could be feasibly emulated using currently available RWE sources in terms of medical claims or structured electronic health record data. The findings of this study suggests that currently available RWD sources and observational methods are unlikely to replace postapproval confirmatory trial requirements as has been proposed in legislative proposals. Moreover, my colleagues also examined whether any US-based clinical trials for novel drugs published in high-impact medical journals could be feasibly replicated using similar RWD sources, finding that only 15% could.[9] Thus, while RWE has demonstrated promise in complementing clinical trial data for medical products, there has not been demonstrated evidence to suggest that

RWE can be used to replace clinical trials and that it may be premature to codify such use under legislation.

a. Do you have any recommendations on how to improve the quality and accuracy of the data received from electronic health records and claims?

Electronic health record (EHR) and claims data were not designed for the purposes of regulatory review, which lends to their limitations in being utilized for this purpose, despite having advantages compared to more costly, complex, and lengthy data collection methods through clinical trials. On one hand, EHR data in its ideal form does include detailed clinical information about patients including demographic information as well as other underlying conditions and prescribed or administered treatments. However, even these advantages may be limited if there is uneven data quality or limited inter-operability across different health systems where patients may be seeking care (e.g. for instance, several of my patients seek care through the Yale New Health System as well as the Veterans Health Administration, which have two completely different EHRs and no mechanism for inter-operability). Additionally, should patients seek care at another health system or provider without inter-operability, longitudinal data around efficacy or safety of a medical product may also be limited.

Moreover, there may be a lag period in certain data elements including other medical conditions or treatments that a patient may be receiving. This is critical for understanding whether the treatment effect seen in an RWE study is attributable to a drug or device product. Other unmeasured confounders – that is, something that could be influencing the patients receiving the product of interest and outcomes of interest but not reflected within the available data – could also be present. Additionally, EHRs very rarely include data on patient-reported outcomes as the data collected is by the clinician or provider such that key information regarding whether a drug or device affected their quality of life, symptoms such as pain or fatigue, or other health behaviors will likely not be reflected in this data source.

Claims data also have similar, potential advantages (provided that patients remain in the same health system or with the same payer over time) in that data collection and abstraction can be fairly simple and efficient. As coding standards even across health systems may be widely accepted, claims data would be fairly consistent. However, claims data do not include detailed clinical information as in EHRs and within such data, there may be difficulty in differentiating patient comorbidities from complications. Additionally, patients may move across health insurers making it difficult to collect longitudinal data for follow-up. There also may be a time lag in the data due to coding typically being completed after the clinical care encounter.

In a recent study conducted by my colleagues, they sought to use RWE in the form of EHR and claims data to emulate a randomized-controlled trial comparing the cardiovascular risk of two prostate cancer drugs.[10] They found that only a quarter of real-world patients using the examined drugs met the randomized controlled trial's narrow inclusion and exclusion criteria. They were also not able to use RWE to precisely emulate the endpoints examined within the randomized-controlled trial. The authors did highlight a few key considerations for enhancing EHRs and claims data in such RWE studies including:

- the need for adequate observational data to emulate clinical trial enrollment criteria and for the evaluation of endpoints, as specific endpoints for this RWE study such as morality due to cancer or whether cardiovascular events were fatal or not were unable to be determined using claims data;
- consideration of whether data allows for adequate follow-up and whether enrollment dates are available within the data source to ensure a sufficient follow-up period, noting that EHRs would not have such dates; and
- the need for comparison to clinical trials to determine whether patient or provider behaviors or other confounding variables may have contributed to the observed findings.

FDA recently issued draft guidance in late October on "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products." With Drs. Joseph S. Ross (Professor of Medicine and Public Health) and Sanket S. Dhruva (Assistant Professor of Cardiology, University of California, San Francisco), we submitted comments on how such guidance could be further strengthened to ensure the integrity of the data towards informing regulatory decisions.[11] Some of these recommendations include:

- **mandatory registration and results reporting of all RWD-based studies of FDA-regulated medical products with prespecification** of data sources, all endpoints, statistical analysis plan, and public reporting of results from all analyses either to coincide with submission for publication or within 6 months of study completion – such registration and results reporting through *ClinicalTrials.gov* are already statutorily mandated for clinical trials under the Food and Drug Administration Amendments Act of 2007, which can be further expanded to include RWE studies;
- **sponsors of RWE studies should submit protocols and statistical analysis plans to FDA before initiating the study** to allow the agency to ensure appropriateness of endpoints, availability of study data within the prespecified RWD sources that would be used, and methods to mitigate the effect of unmeasured confounders that could obscure the observed study findings;
- **inter-operability of RWD sources including EHRs across health systems and organizations** to limit the presence of missing data including for follow-up and overcounting the same patients who may be seen across different health systems as well as to allow for longitudinal data for

adequate follow-up of patients who may move their care to a different health system after a period of time;

- **RWD sources such as EHRs should contain adequate numbers of patients with adequate follow-up for outcomes of interest**, but such that follow-up would entail consistent measurement of the outcomes of interest (one example we included as part of our comments to FDA was that of a patient receiving a drug for cardiovascular disease with follow-up at one year for safety and efficacy; it is possible that the EHR would show that the patient sought follow-up care at one year, but at a non-cardiovascular or other relevant clinic, which should not be considered as adequate follow-up);
- **RWD should include accurate and updated information of both prescription as well as non-prescription drugs and those are not reimbursed by payers** that if either not updated or included, would confound any observed findings;
- **RWD sources should account for missing data often not captured within EHR or claims data** including tests or treatments either not ordered, ordered but not conducted/received, conducted/received but not reflected in the data sources, or where data is just not available; and
- **validation of outcomes collected and abstracted from RWD sources, particularly proxy measures that meant to be reflective of endpoints collected in clinical trials** as there may be heterogeneity in how these proxy measures are collected.

Ideally, Congress should mandate medical product sponsors to register RWE studies including their protocols onto a public database such as ClinicalTrials.gov (or other publicly accessible database) as they are required to do with clinical trials. Congress should also mandate sponsors to report RWE study results onto ClinicalTrials.gov (or other publicly accessible database) in a timely manner as described above. FDA should also be given enforcement authority to ensure compliance with registration and reporting as they have with clinical trials. Sponsors should also be required to collaborate with the FDA in establishing their RWE study protocols to ensure oversight and integrity of the RWD sources, collection, and abstraction.

b. How can we be encouraging better data collection at the point of care with regulatory decision-making in mind?

Infrastructure investment to allow for better and sufficient data collection at the point of care will be needed. As mentioned earlier, EHRs, which would be the primary source of point-of-care clinical care information as well as claims data were not designed for the purposes of regulatory decision-making or clinical research. Enhanced data collection at the point of care must also be balanced with time constraints for clinicians and other providers as well as patients in making clinical care decisions. FDA is exploring the use of artificial intelligence and machine learning towards this goal and to leverage other unstructured sources of

data. However, engagement of patients, clinicians, and other providers to examine the real-world impacts of data collection methods and their impact on clinical care will be needed. These stakeholders can provide valuable insight in how to seamless integrate the accurate collection of data elements necessary for a robust RWE study at the point of care without increasing their resource burden in doing so.

As a first step, requiring that sponsors submit their protocols to FDA for RWE studies ahead of initiating them would allow the agency to examine the RWD sources to determine specific considerations for data collection including the need for additional or substitute proxy measures. Ideal data sources would not only include clinician-entered clinical data, but also those that are patient-reported and patient-generated. For collecting such data from patients in an efficient manner, opportunities to engage patients outside of the clinical care setting are being piloted including through mobile applications from health systems and organizations and tele-health. However, validation of such data by the FDA is necessary to ensure an accurate association with meaningful clinical outcomes. Quality control measures must also be in place to ensure data validity. Finally, training of clinicians and other providers to ensure consistency and accuracy of data collection as well as to prevent against heterogeneity in data reporting.

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