Attachment—Additional Questions for the Record

Subcommittee on Health
Hearing on
" The Future of Medicine: Legislation to Encourage Innovation and Improve Oversight "
March 17, 2022

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The Honorable Michael C. Burgess, M.D. (R-TX)

1. To build off 21st Century Cures Act, I introduced the FDA Advancing Collection of Transformative Science (FACTS Act). The FACTS Act will help cut red tape to create efficiencies and streamline the transition between an emergency use authorization (EUA), premarket submission, and permanent marketing authorization, all without cutting corners or jeopardizing safety requirements. Our nation has experienced a historical response in the development of therapeutics and vaccinations to combat this virus. In fact, Dr. Fauci advised that it would be at least one year until Americans would receive a COVID-19 vaccine. Well, here we are today with two vaccines and many effective therapeutics. It has truly been history in the making. However, it is also important that the FDA utilizes data generated from patients using effective therapeutics and vaccines that have been granted through EUA process. The FDA should be taking this data into consideration. It is no secret that one of the FDA's commitments is related to enhancing the way that we use real world data.

    a. How can real world evidence be used to complement clinical trials?

Randomized control trials (RCTs) are designed to provide evidence of drug efficacy and are the gold standard for comparing treatments. However, there are circumstances where a randomized control trial is not possible (e.g., rare diseases and other disease/therapeutic areas with small patient populations). In those circumstances, the use of real-world evidence can be used as an external control arm in the clinical trial to estimate the comparative treatment effect of the drug.

    b. Should there be any guardrails on the safety and utilization of real-world evidence?

The 2018 Framework for FDA's Real-World Evidence Program provides guardrails on the safety and utilization of real-world evidence. This framework specifies a three-part approach to evaluating the potential use of RWE to support changes to labeling about drug product effectiveness:

a. Whether the RWD are fit for use
b. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question, and
c. Whether the study conduct meeting FDA regulatory requirements (e.g., for study monitoring and data collection)

Hence, this approach highlights the regulatory considerations and guardrails in leveraging real-world data to support regulatory decision making.

c. Are there ways that we can improve and modernize the way we collect data from electronic health records and claims?

Yes, there are ways that we can improve and modernize the way we collect data from electronic health records and claims. Recently, FDA published draft guidance on Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products. In response to this draft guidance, BIO highlighted the need to identify best practices for data curation, processing and governance. Our recommendation included FDA working with stakeholders to better understand and address the practical realities of data curation, processing and governance as FDA is in the unique position to bring together all of the relevant stakeholders to understand the expectations for real world data (RWD) quality. It is imperative to work with health technology organizations that generate RWD and host workshops with all stakeholders to better understand these issues and help identify ways to meet Agency expectations.

d. Do you believe real world evidence promotes and advances personalized medicine for individuals and for the population at large? Can you explain how this works and how it will affect public health overall?

Yes, real world data and evidence have the potential to promote and advance personalized medicine for individuals and for the population at large. By definition, real world data are data relating to patient health status and/or the delivery of health care routinely collected from variety of sources and real world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real world data. Having a more robust understanding of how a drug or treatment works in the real world setting can help support approval of new indications for drugs or help support or satisfy post approval study requirements which can provide patients more timely access to innovative medicines.

e. Do you believe that implementing real world evidence techniques into the FDAs regulatory body will help advance innovation in oncology and the rare disease world?

Yes, the use of real world evidence to support FDA's regulatory decision making will help advance innovation in drug development, including in oncology and the rare disease space. For rare diseases and other disease/therapeutic areas that

have small or limited patient populations such as pediatrics, conducting a traditional clinical trial is not feasible and/or unethical. Hence, the use of real world data and evidence, offer patients hope for the promise of new and innovative medicines.

2. While the FFDCA makes clear that the FDA has the authority to approved drugs that not only treat disease but also prevent disease, the FDA historically has taken a very conservative approach to approving preventive products – even suggesting in the past that preventive products should face a higher evidentiary bar than traditional products that treat people after they become sick. Yet the ability to prevent disease, or the progression of disease, seems as important, if not more important, than treating disease after it has taken hold in a patient's body. Indeed, costs are higher, and outcomes are worse the longer it takes to catch and intervene against disease.

    a. Does the FDA still believe that preventive products should face a higher approval bar, and if so, why?

All products developed to prevent disease are reviewed by the FDA and held to the same evidentiary standards for safety and effectiveness as those products developed to treat disease. In the example of the use of aspirin for primary prevention of heart attack and stroke, FDA did find that the available evidence supported the use of aspirin for *secondary* prevention of heart attack and stroke, meaning that aspirin could prevent another heart attack or stroke in patients who have already had a heart attack or stroke. More recent examples such as for prevention of migraines, HIV infection and post-exposure prophylaxis for prevention of COVID-19 demonstrate the FDA's efforts to approve drugs to prevent disease.

3. Under the Accelerated Approval pathway, the FDA has the authority to rely on both surrogate and intermediate endpoints to predict likely clinical benefit for patients with serious unmet medical needs, rather than delaying approval until confirmatory trials can be completed that conclusively show clinical benefit.

    a. While surrogates like tumor shrinkage in cancer patients are a typical basis for Accelerated Approval, what other methods does the FDA permit sponsors to use in terms of predicting likely clinical benefit, particularly when involving preventive products whose clinical benefit is preventing the onset or progression of disease? And has the FDA considered the ability to rely on advanced technologies such as AI, machine learning, and advanced computational and analytical techniques to aid in the predictive analysis?

The FDA defines "clinical benefit" as a positive therapeutic effect that is clinically meaningful in the context of a given disease. For Accelerated Approval, phase 4 confirmatory trials are conducted by the sponsor to confirm the clinical benefit. Other

surrogate endpoints that have been the basis for accelerated approval include, but are not limited to:

- Prolonged suppression of HIV viral load in plasma has been shown to reduce the morbidity and mortality associated with HIV disease and has been the basis for Contains Nonbinding Recommendations 18 traditional approval. Shorter-term suppression of viral load has been used in the past as a surrogate to support accelerated approval because it was considered reasonably likely to predict an effect on morbidity or mortality. Data now demonstrate that short-term suppression of viral load may support full approval, in some circumstances.
- Clearance of bacteria from the blood stream as evidenced by a laboratory measurement of bacteria in the blood has been considered reasonably likely to predict the clinical resolution of infection.
- Outcomes of 6-month follow-up treatment (i.e., sputum culture status and infection relapse rate) have been considered reasonably likely to predict the resolution of pulmonary tuberculosis.
- Decrease in iron stores for patients with iron overload caused by thalassemia has been considered reasonably likely to predict a decrease in transfusion-related adverse events caused by iron overload in the body.
- Radiographic evidence of tumor shrinkage (response rate) in certain cancer types has been considered reasonably likely to predict an improvement in overall survival.

The PDUFA VII Commitment Letter includes provisions for a pilot Advancing the RWE program which specifically highlights the use of RWE in postapproval studies. Also, within the PDUFA VII Commitment Letter are provisions around enhancing the use of digital health technologies (DHT) in drug development and review. These provisions provide FDA with the resources to establish a DHT framework to guide the use of DHT-derived data in regulatory decision making for drugs and biological products. These provisions afford the FDA the opportunity to have workshops, conduct demonstrations products and issue guidance on use of DHTs. These PDUFA VII provisions will allow FDA to better consider ways to rely on advanced technologies such as AI, machine learning, and advanced computational and analytical techniques to aid in the predictive analysis.

<u>The Honorable Earl L. “Buddy” Carter (R-GA)</u>

1. Dr. Esham, would you explain how H.R. 7032, the “Increasing Transparency in Generic Drug Applications Act,” could limit patient access to new therapies by forcing companies to divulge highly valuable trade secrets?

BIO supports innovation in drug development to improve patient access to new and innovative medicines. Forcing companies to divulge highly valuable trade secrets may create disincentives in the marketplace that could adversely limit patient access to new therapies. Hence, it is important to fully understand what the problem is that HR 7032 is trying to address and making sure that we take into account existing Hatch-Waxman and BPCIA provisions.