February 5, 2019

Scott Gottlieb, M.D.
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2018-N-4000, Framework for a Real-World Evidence Program

Filed electronically at http://www.regulations.gov

Dear Commissioner Gottlieb:

On behalf of the Cystic Fibrosis Foundation, we write to provide comments in response to the FDA's Framework for a Real-World Evidence (RWE) Program. We appreciate the opportunity to share our thoughts on this document and commend the Agency for taking steps to address the significant number of unknowns in applying RWE in regulatory-decision making through guidance and standards setting.

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis – a rare genetic disease that affects over 30,000 people in the United States. The CF Foundation has been engaged in virtually every element of the research and development process, from preclinical discovery to identification of new therapeutics to conducting clinical trials as well as post-market surveillance and quality improvement studies.

While we have been fortunate as a community to have made great progress in the development of effective therapies for many people with CF, we are not yet done. The CF Foundation is dedicated to improving the quality of life and standard of care for individuals with CF. To aid this end, the Foundation maintains a patient registry to collect information on the health status of people with cystic fibrosis who receive care at CF Foundation-accredited care centers.

The CF Foundation patient registry is a unique and rich source of real-word data (RWD) containing information dating back to 1986. This data is leveraged for a number of purposes including developing CF care guidelines, guiding quality improvement initiatives at care centers, and optimizing standards of care in an age of disease-modifying CF drugs. Additionally, patient registry data is used to support phase IV post-marketing requirements. RWE holds promise for advancing CF drug R&D through uses in hybrid studies, single arm trials, label expansions and more. However, we believe it is important to move forward in a thoughtful manner in applying RWE in regulatory decision-making. RWE has limitations that must be acknowledged, and the capabilities of this data must be further assessed to ensure study

outcomes are valid and reliable. The following comments reflect our substantial experience with collecting and utilizing RWE to advance care for people with CF.

Role of Risk Tolerance in RWE Standards

The FDA should be mindful of population differences in risk tolerance as they consider what standards are required for RWE used in the regulatory process. Given that RWE has the potential to have a more immediate value to patient populations suffering from severe conditions with little to no existing therapeutic options, it is important to consider the needs of these populations throughout the FDA's RWE Program activities. We ask the FDA to extend Agency thinking on population risk tolerance impacts to safety and efficacy standards for randomized controlled trials to applications of RWE.

Electronic Health Records (EHRs)

It is important that the FDA acknowledges the challenges that remain in establishing EHRs as a consistently reliable and valid source of RWE. While EHR data is promising, there remains a substantial amount of unanswered questions on how to reconcile lack of interoperability between providers and care sites, lack of standardization with clinician-entered data such as symptomatic changes and disease manifestation, and inconsistently captured health-related variables. We recognize that these issues extend beyond the regulatory context, as EHRs are first and foremost tools designed for recording patient care by individual care providers and facilities. More guidance will be needed to ensure RWD drawn from EHRs is adequate for regulatory use.

In developing further guidance on EHR data use, the FDA should consider what kinds of outcomes lend themselves to being readily accessed via EHRs as well as what types of data are trustable when sourced through EHRs and what types are not. For example, while discrete data on procedures and hospitalizations are relatively easy to obtain through EHRs, descriptive information about symptoms or treatment performance may be more challenging to collect. It may therefore be more appropriate to source such information through other RWD collection methods. The FDA should further assess what types of regulatory questions are more likely to be adequately addressed via EHRs compared with richer data sources as well.

Patient Registries

We appreciate the Agency's acknowledgment that registries must have processes for ensuring the RWE generated is reliable, such as methods for ensuring data quality and the ability to gather follow-up information as necessary. However, more guidance is needed to establish methods for assessing the relevance and reliability of patient registry-generated RWE.

Patient registries can aid in evaluating the effectiveness of new therapies when well standardized and validated, especially for rare disease populations where traditional randomized, placebo-controlled clinical trials may not be practical or feasible. Patient registries are not necessarily a cleaner source of data than EHRs, however. Due to the range of registry content, variations in data collection methods, and differences in driving purposes or goals, it will be difficult to uniformly compare data quality and set data standards across patient registries.

The source of patient registry data is particularly impactful on the content. In developing guidance around registry-generated RWE, it may be better to think about registries in relation to where the data comes from. For example, registry data sourced from EHRs will likely have similar capabilities and limitations as RWD drawn directly from EHRs. Registries developed for collecting patient experience and patient reported data will likely reflect limitations and capacities of data drawn from similar sources.

It is important for the FDA to consider the differences in legacy versus newly formed registries when developing standards for registry-sourced RWD. FDA standards for source document verification and auditing should be context dependent. Legacy registries can provide hard to find historical data of a condition and can shed light on how changes to standards of care can impact disease manifestation and progression. However, legacy registries may not be able to trace source documentation to the extent that newly established patient databases can. FDA standards for auditing and source document verification should not inhibit the use of otherwise valid legacy data sources that can provide valuable, hard to get information. These considerations should also apply to registries that deal with rare disease-specific patient populations, which often have few if no alternative RWD sources. We urge the FDA to consider what level of verification is sufficient and feasible for different types of registries.

Single Arm Trials with External Real-World Data Controls

RWD from patient registries, EHRs, or other sources can serve as historical data in a trial where relevant controls from prior clinical trials may not be available. This data can fill an important need in drug development, in particular with studying populations where placebo controls may not be ethical or feasible. Changes in standards of care over time and lack of standardized data collection can pose challenges to the application of historical RWD, however. More guidance is needed to establish practices for evaluating if historical population data intended for use in clinical trials is appropriately comparable to the current population being studied. We request the FDA move forward with guidance on using RWD to generate external control arms to address concerns such as these.

Observational Studies

The FDA framework raises concerns with regard to retrospective observational study validity. The planned guidance to address reporting and methodological standards will be important to ensure appropriate use of this RWE tool. Meta-analysis may need to be more heavily relied on to help replicate study findings in these instances, and it may therefore be worthwhile for the Agency to address the role of this tool in the observational study guidance. In thinking about reporting standards, the FDA should consider how the competing interests of administrative burden and transparency will be balanced.

Guidance and standards for determining validity of observational study findings will likely be needed for smaller rare disease patient populations as well as for larger patient populations. With rare disease patient populations, there may not be alternative RWD sources that can be leveraged to confer findings. Furthermore, guidance for rare disease populations can be particularly valuable here since such populations are more likely to embrace alternative sources of data where more traditional clinical trials are not feasible.

Regulatory Use of RWE in Initial Product Approvals

While this framework is focused predominantly on product extensions, it is important to note that there may be situations when it is appropriate or necessary to use RWE to support initial product approval. The FDA has raised this use of RWE in other guidances, especially with regard to rare disease drug development. We understand that while this is outside of the scope of this framework, we ask the FDA to be mindful of how RWE Program activities may impact RWE applications in initial product approvals.

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Once again, we commend the FDA for making efforts to advance regulatory use of RWE through the Agency's Framework for a Real-World Evidence Program. For people with CF and other rare diseases, RWE holds promise in addressing inherent challenges in rare disease drug development. We welcome an ongoing dialogue with the FDA as the Agency continues to evolve its thinking on RWE in regulatory decision-making.

Sincerely,

Mary Dwight

Senior Vice President of Policy and Advocacy
Cystic Fibrosis Foundation