Reality Check: FDA Draft Guidance Outlines Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drugs and Biological Products

 Last week the FDA issued another draft guidance in its series of recent guidance documents setting forth the agency's views regarding the generation and use of Real-World Data (RWD) and Real-World Evidence (RWE) for prescription drugs and biological products. (see our **recent post** on FDA's draft guidance relating to registries).

This latest draft guidance, **Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products**, clarifies the agency's expectations for sponsors submitting new drug applications (NDAs) or biologics license applications (BLAs) with studies using Real-World Data (RWD) to support the safety or effectiveness of drugs or biological products, when such studies are not subject to FDA's investigational new drug (IND) application requirements under **21 CFR Part 312**. The draft guidance focuses on non-interventional (*a.k.a.* observational) studies, in which patients receive a drug during routine medical practice, according to a medical provider's clinical judgment and based on patient characteristics, rather than via assignment to a study arm and according to a clinical trial protocol.

Key considerations outlined in the guidance:

- *Sponsors designing a non-interventional study to support a marketing application should engage early with the relevant FDA review division* (e.g., through a Type C meeting) and be prepared to submit draft protocols and SAPs for FDA feedback *before* conducting the study analyses.

- *To assure the FDA that the results of a non-interventional study were not skewed to favor a particular conclusion,* sponsors should provide evidence that the non-interventional study protocol and statistical analysis plan were finalized *prior* to reviewing outcome data and *before* performing prespecified analyses. Sponsors should provide a justification for selecting relevant data sources and generate audit trails in their datasets. FDA also recommends that sponsors post their non-interventional study protocols on a publicly available website, such as **ClinicalTrials.gov**.

- *Sponsors must be able to submit patient-level data from the RWD.* Where a third party owns or controls the RWD, sponsors should have agreements with such parties to ensure that patient-level data and source data to verify the RWD can be provided to the FDA for inspection, as applicable. Sponsors should have well-documented programming codes and algorithms that would allow the FDA to replicate the study analysis using the same dataset and analytic

approach.

- *Non-interventional studies should be monitored.* The FDA advises sponsors to use a risk-based quality management approach, with a focus on preventing or mitigating important and/or likely risks to study quality. If a non-interventional study does not include any activities or procedures involving patients, monitoring can focus on assuring the data integrity of the RWD, from extraction to analysis to reporting of results. When a non-interventional study protocol includes ancillary activities or procedures, sponsors should exercise appropriate oversight of processes critical to human subject protection.

- *Adverse events that a sponsor becomes aware of through a non-interventional study must be submitted in accordance with postmarketing safety reporting regulations*. However, the agency acknowledges that if a sponsor is conducting a non-interventional study that appropriately utilizes only a subset of a larger dataset, the sponsor will not have to search the entirety of the dataset for adverse events.

- *Sponsors should take responsibility for all activities related to the design, conduct and oversight of a non-interventional study that is being submitted for regulatory review*. This includes selecting qualified researchers, ensuring the study is conducted in accordance with the protocol, maintaining and retaining adequate study records, and maintaining an electronic system to manage RWD that complies with **21 CFR Part 11**. Where a sponsor engages third parties to perform certain study-related tasks, the responsibilities of each organization should be documented and made readily available to the FDA upon request.

Comments on the guidance should be submitted to the docket by March 9, 2022.