FDA Releases Two Guidances for Innovative Drug Development

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On September 28, 2018 the U.S. Food and Drug Administration (FDA or Agency) issued two draft guidance documents focusing on clinical trial designs to advance drug development and competition. Both documents aim to streamline the clinical trial process by lowering development costs, as part of Commissioner Scott Gottlieb's continuing efforts to promote competition and accelerate patient access to innovative new drugs. Taken together, they offer important insights for sponsors of novel therapies, including gene therapies for rare disease indications and cancer immunotherapies.

Adaptive Designs for Clinical Trials of Drugs and Biologics

The first draft guidance, Adaptive Designs for Clinical Trials of Drugs and Biologics, provides foundational principles as well as procedural advice to sponsors and applicants submitting Investigational New Drug applications (INDs), New Drug Applications (NDAs), Biologics Licensing Applications (BLAs), and supplemental applications.

In a September 28 speech, Commissioner Gottlieb noted the potential of adaptive designs to "improve ... study power and reduce the sample size and total cost" for investigational drugs, including "targeted medicines that are being put into development today."

Adaptive designs allow for changes to a clinical trial based on data generated as the trial proceeds. As the draft guidance notes, adaptive designs afford several advantages, ranging from statistical efficiency by providing a greater chance to detect a true drug effect, to ethical considerations such as the ability to halt a trial early if the drug is unlikely to demonstrate effectiveness, as well as enhanced stakeholder acceptability from potential assignment to treatment. The guidance illustrates these advantages with specific examples of actual clinical trials with adaptive designs, including HPV vaccine and Ebola therapy.

Despite these advantages, there are limitations that may arise from adaptive designs. An adaptive change may lead to results that are not similar to those before the adaptation. Moreover, the increased complexity of some adaptive trials and uncertainties may warrant earlier and more extensive interactions with the FDA than usual. Therefore, the Agency notes “it is not the intent of this guidance to require or restrict the use of adaptive designs,” but, rather, encourage the sponsor to explore and discuss a variety of design options with FDA.

The 32-page draft guidance addresses critical adaptive design considerations related to sample size, patient population, and treatment arm and endpoint selection. Just as important, the guidance proposes design principles to maintain clinical trial integrity and discusses sponsor-Agency interactions. In particular, the guidance discusses the use of end-of-phase-2 (EOP2) and Type C meetings and the internal challenges of assessing proposed, potentially more complex adaptive designs.

Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

The second draft guidance on Master Protocols proposes recommendations on how sponsors can design and conduct clinical trials intended to evaluate more than one investigational drug and/or more than one cancer type simultaneously within the same overall trial structure for adult and pediatric cancers. In contrast to traditional trial designs, in which a single drug is tested in a single disease population in one clinical trial, master protocols, often termed as “umbrella” or “basket” protocols, simultaneously evaluate multiple drugs and disease populations in multiple sub-studies.

Commissioner Gottlieb cited chimeric antigen receptor therapy (CAR-T) therapies as exemplary of how a basket trial "could allow

multiple rare B-cell malignancies to be tested using a single CAR-T therapy" enabling "sponsors to develop evidence that supports approval of the therapy against multiple malignancies in a single trial."

The complexities of master protocols lead to complex requirements for IRB reviews and informed consent forms. As the FDA notes, "[t]o facilitate IRB review of master protocols, [the Agency] recommends the use of a central IRB . . . [with] adequate resources . . . to assist in the review of complex issues . . ." Furthermore, in addition to submitting informed consent forms to the IRB for review, a sponsor may need to submit the original and all updated documents to the IND to allow FDA to assess that patients have the information to make informed decisions regarding trial participation.

In addition to extensive design, statistical, and safety considerations, the Agency briefly discusses when the use of a biomarker may be appropriate. FDA has historically encouraged the use of biomarkers to facilitate the development of medical products, and the guidance discusses aspects of master protocol designs related to biomarker development and advises sponsors on how to submit such information to FDA to facilitate efficient review.

Next Steps

The draft guidances reflect the FDA's extensive interactions with sponsors, investigators, patients, and other regulatory agencies. These draft guidance documents, among others issued by the Agency, would provide greater clarity, if finalized, about FDA's approach to product development. FDA is accepting comment on the proposed guidances through November 30, 2018. Comments may be submitted in writing and mailed to: Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852 or electronically uploaded through https://www.regulations.gov (Docket No. FDA-2018-D-3124).

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