September 30, 2019

Ned Sharpless, MD
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: FDA-2019-D-3049, E8(R1) General Considerations for Clinical Studies; International Council for Harmonisation; Draft Guidance for Industry

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

Dear Acting Commissioner Sharpless:

On behalf of the Cystic Fibrosis Foundation, I write to provide comments on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) draft guidance entitled *E8(R1) General Considerations for Clinical Studies; International Council for Harmonisation; Draft Guidance for Industry* (July 2019). We appreciate that the FDA, along with other regulatory authorities and industry representatives across the globe, has signaled the importance of modernized clinical trial designs in updating this important document.

Background on cystic fibrosis and the CF Foundation

The Cystic Fibrosis Foundation is a national organization actively engaged in the research and development of new therapies for cystic fibrosis (CF) – 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.

The CF Foundation has significant experience with the process of rare disease drug research and development. When the Foundation was formed in 1955, no CF-specific drugs existed. However, by raising and directing funds needed to fuel CF drug development programs, the Foundation has encouraged pharmaceutical companies to invest in rare disease research. Additionally, with the Foundation's Therapeutics Development Network (TDN) – the largest CF clinical trials network in the world – we have been able to spur clinical trial designs that work for the CF community. Today, there are 13 therapeutic products available to treat people with CF, three of which treat the underlying cause of the disease. Our comments provided below reflect our substantial experience and observations in the rare disease drug development space.

Special considerations for rare disease populations

We have appreciated FDA's ongoing efforts to provide updated advice to sponsors on the unique challenges inherent in rare disease drug development. However, while this guidance acknowledges many clinical trial design innovations important to modern rare disease therapeutic development, the ICH guidance fails to directly address the distinct characteristics and needs of rare disease populations and how such factors may impact the design of clinical trials.

The ICH guidance should reflect the needs of rare disease communities and call out the need for special considerations when dealing with rare disease populations. When looked at individually, rare diseases affect seemingly small and discrete communities. However, the total number of individuals impacted by rare diseases is anything but negligible. In total, there are upwards of 7,000 rare diseases impacting an estimated 25-30 million individuals in the US alone.[1] One of the highest areas of unmet medical need is in the rare disease arena, as the vast majority of rare diseases have no treatments available at all.

Successful legislative strategies in the US, namely the Orphan Drug Act, as well as scientific advances have encouraged a substantial number of companies to invest in therapeutic development for rare disease populations with major unmet needs. We have seen the therapeutic pipeline grow drastically in recent years for CF as well as for a number of other rare diseases. With over 500 orphan drug therapies approved in the US and more than 140 orphan medicines authorized in the EU,[2] rare disease drug development is no longer simply a niche topic.

Rare disease communities often face unique challenges such as small patient populations, poor disease characterization, and wide range of disease presentation that make it more difficult to carry out traditional clinical trials. FDA innovations in regulatory science, modernization of clinical trial designs, and increasing emphasis on the importance of patient input have all been critical in addressing the many challenges rare disease drug development programs face. Regulatory flexibility has also played an important role in evaluating new therapies for rare diseases in the US.

Small population size in particular can create a fairly onerous barrier for rare disease clinical trials. Rare disease trials may need to access populations of patients from around the globe in order to overcome small patient pools in any given country. Therefore, there may be an even higher need for international recognition and harmonization on accepted practices for rare disease clinical trial designs compared with larger patient populations.

The ICH should consider adding rare disease populations to the section titled *Consideration in Special Populations* found on page 14 of the guidance document. Like other populations listed under this section, clinical research in rare disease populations requires special considerations that may differ from the general population. Regulatory authorities and drug sponsors should be mindful of population differences in risk tolerance, the need for flexibility in trial designs where traditional studies may not be feasible, and other characteristics unique to rare disease populations that may impact drug development and regulatory review for products targeted towards these populations.

[1] https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases retrieved 9/23/2019
[2] https://www.ema.europa.eu/en/documents/leaflet/leaflet-orphan-medicines-eu_en.pdf retrieved 9/24/2019

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Once again, we thank the FDA for its request for comments on this revised draft guidance document. The international regulatory community's efforts to harmonize modern clinical trial design practices will be critical for advancing rare disease drug development, and we look forward to working alongside the FDA in the future on this endeavor.

Sincerely,

Mary Dwight
Senior Vice President of Policy and Advocacy
Cystic Fibrosis Foundation