Treatment Action Group

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Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
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Re: Public Comment for Draft Guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (Docket No. FDA-2019-D-4964)

Treatment Action Group (TAG) welcomes the opportunity to provide commentary on the FDA's Draft Guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (Docket No. FDA-2019-D-4964). TAG is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

TAG supports the FDA's efforts to expand its guidance on acceptable trial designs in recognition of the many challenges to advance timely research for rare and serious diseases while ensuring that the highest possible standards of rigorous research are adhered to. However, we have concerns that the document as written may move us too far away from the historical standard of ensuring that trials are "well-controlled" and may unnecessarily sacrifice research quality for the wrong reasons and limited public benefit. For example, lines 532 through 536, which state that an increase in false positive conclusions "may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy," leave the impression that the guidance is placing market interests over quality science.

As industry stakeholders– and the patient advocacy groups they fund– continue to aggressively promote a deregulatory agenda in order to expedite trial timelines, cut costs, and increase the speed of market entry and resultant revenues, we are concerned about the potential negative downstream effects. This risk is that we will end up with more and more products on the market that we know less and less about, at best squandering precious public resources on products with limited benefits, and at worst endangering the public the FDA serves to protect.

Those who back the deregulatory position justify their efforts by claiming that the FDA is a roadblock to progress and that regulatory inefficiencies and bureaucratic agency requirements are preventing sick people from accessing the treatments and cures they desperately need. Yet, the FDA has set the global standard for efficient, predictable, and rigorous regulation with a

track record of rapid and timely approvals for new drugs and biologics. Extant mechanisms for preapproval access could be further strengthened if the FDA were authorized to require and standardize company policies and processes. Extant FDA regulatory and pre-approval access mechanisms work well; the answer isn't lowering the bar but supporting more companies to clear it, including by providing guidance that makes clear when flexibilities are warranted, and how to operationalize them while maintaining scientific rigor.

Several points in the document have the potential to dramatically and unnecessarily deviate from rigorous research standards. Below, we highlight several examples of concern:

- *Use of external and historical controls*

Lines 248 through 250 state that "compelling results may overcome challenges associated with less rigorous trial designs, such as those with an external control." In general, the document seems to overly facilitate the use of external or historical controls, which have the potential to produce significant bias in trial results. While compelling results may allow for approval of a new compound or agent, this particular text fails to state that there is still an increased danger that we may falsely conclude that an ineffective treatment is effective. Also, we will be unable to pinpoint exactly how effective a new therapy is. This can have profound implications in fields like HIV prevention, where the difference between a 30% or 60% effective modality matters in terms of acceptability, population rollout, and public trust in science.

While lines 231 through 237 clearly outline what is ideal in terms of an external control, we are concerned how this loose guidance will translate into practice. One recent concerning example is Gilead Sciences' use of an external control to support findings of the Discover trial; in that case the demographic make-up of the RCT looked markedly different compared to the external control population.[1]

- *Flexibilities in situations of unmet medical need*

Section V, "Examples of clinical circumstances where additional flexibility may be warranted" offers flexibilities and exceptions for instances of unmet medical need or when a disease is considered rare. There is however no mention of the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD pathway), a regulatory mechanism dissimilar to accelerated approval and other extant pathways that allow for temporary drug approvals in response to urgent unmet medical need on the condition that additional research to address uncertainties will be conducted.

A recent example of what these flexibilities and exceptions look like in practice is the TB Alliance's use of the LPAD pathway for pretomanid in the context of the three-drug Nix-TB regimen (pretomanid, bedaquiline, linezolid) for the treatment of extensively drug-resistant

[1] Treatment Action Group. https://www.treatmentactiongroup.org/statement/following-restricted-fda-approval-of-descovy-as-prep-tag-calls-on-gilead-to-immediately-partner-with-community-for-research-on-vaginal-exposure/

(XDR-), and treatment intolerant or non-responsive (TI/NR) multidrug-resistant TB (MDR-TB). In this instance the external control was non-concurrent and excluded all people who received treatment with bedaquiline or linezolid – two of the three drugs included in the Nix-TB regimen and the backbone of regimens currently recommended by the World Health Organization for drug-resistant TB. Pretomanid was approved by the FDA, but its relative contribution to the Nix-TB regimen remains ambiguous.[2,3]

- *Use of non-clinical data*

Line 411 states support for including non-clinical data as confirmatory evidence for efficacy of a new treatment; we are concerned that this document does not properly stress the significant limitations of this sort of evidence. Non-clinical data can perhaps support a large, well-controlled RCT, but it cannot substitute for large trials or bolster a smaller trial with significant opportunities for bias.

- *Non-inferiority designs*

Lines 205–208 state that "[non-inferiority] designs are credible and appropriate only in situations in which the active control has shown a consistent effect (generally compared with placebo) in prior superiority trials…" However, in the context of TB clinical trials, for which we lack reliable surrogate markers for clinically relevant endpoints, and in which even incremental gains can significantly improve the standard of care, non-inferiority trials are the norm. As such, we recommend the guidance take a more nuanced approach to the credibility and acceptability of non-inferiority designs.

The document would be significantly improved with strong, bolded language that makes clear that two adequate, well-controlled trials, or perhaps one large well-controlled multi-center RCT, remain the gold standard for proving efficacy and that all efforts to stick to this standard must be made before proposing an alternative design with external controls and non-clinical data that introduce the possibility of significant bias. Additionally, the document must make clear that the financial cost of conducting a trial cannot be a primary factor in deciding upon an alternative trial design; the flexibilities outlined in this guidance should only be considered in order to avoid potential ethical tensions and overly stringent requirements to determine statistical significance.

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[2] Global TB Community Advisory Board. Research, Regulatory, and Access Considerations Regarding Pretomanid. May 15, 2019. http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_considerations_final_05.14.19.pdf.

[3] Treatment Action Group. Testimony re: docket number FDA-2019-N-1317. https://www.treatmentactiongroup.org/wp-content/uploads/2019/05/TAG_oral_testimony_FDA_pretomanid_hearing_6_5_19.pdf.

Undoubtedly, there are ethical considerations that must necessarily lead to adaptive trial designs in order to balance the need of developing new therapies with legal or moral obligations to trial participants; or to establish a more reasonable standard for achieving statistical significance. Flexibility in trial design is essential in order to maintain development of new tools, however we can be flexible without losing scientific rigor. We are in support of fostering innovation, particularly in the case of urgent or rare diseases, but the public deserves and has a right to know if the therapies they are putting into their bodies are truly effective, especially in the case of urgent or rare diseases.