Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20903
September 11, 2023
[Submitted Online]

Re: Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry [FDA-2023-D-0559]

Thank you for the opportunity to comment on this FDA proposed guidance for industry. We, the undersigned, have reviewed the draft guidance and are writing to express our support for establishing clear standards for good cause of noncompliance for holders of applications (hereafter, sponsors) for human prescription drugs who are required to conduct postmarketing studies or clinical trials under section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act. These postmarketing studies are required at the time of approval or during the postapproval period should the FDA become aware of new safety information, including new information about a serious risk or an unexpected serious risk associated with the use of the drug, or the effectiveness of the approved risk evaluation and mitigation strategy (REMS) for the drug since its most recent assessment. Therefore, these studies provide critical information not only to FDA and sponsors, but also to the clinicians prescribing these drugs and the patients who receive them.

We understand that section 505(o)(3)(E)(ii) requires a sponsor to provide certain information to FDA about its postmarketing studies, including a timetable for study or clinical trial completion, including a final protocol submission date, a study or clinical trial completion date, and a final report submission date, as well as periodic reports (typically annually) on the status of the study or clinical trial.

We also understand that there are reasonable explanations for sponsor noncompliance with the milestones established between them and the FDA for these postmarketing studies, including circumstances beyond the sponsors' control that could not have been reasonably anticipated and factored in at the time the original PMR timetable was finalized. The proposed guidance document for industry offers numerous examples of both reasonable and non-reasonable explanations, which is appreciated.

Nevertheless, we believe the guidance could be further strengthened by establishing clear and transparent mechanisms by which noncompliance with postmarketing requirement milestones, and explanations for noncompliance, are reported publicly.

In our cross-sectional analysis of postmarketing requirements for all new drugs and biologics approved by the FDA between 1 January 2009 and 31 December 2012, with follow-up up to 15 November 2017 (BMJ 2018;361:k2031. Available at: https://www.bmj.com/content/361/bmj.k2031), we made several key observations that relate to this proposed guidance for industry:

Insufficient information is available about 505(o)(3) postmarketing studies and clinical trials. Between 2009 and 2012, the FDA approved 110 new drugs and biologics for 120 indications. We found 437 postmarketing requirements associated with these 97 new drugs and biologics. The median number of requirements per approval letter for each new drug or biologic was four (interquartile range 2-6). Half

the postmarket studies required (220 (50.3%)) were for "new animal or 'other' studies", and nearly one third were for prospective cohort studies, registries, and clinical trials (134 (30.7%)). In terms of relevance to this proposed guidance, more than three quarters of postmarket studies were issued under the FDAAA authority (344 (78.7%)). Critically, individual postmarket study descriptions were often short and difficult to categorize, with a median of 44 words (interquartile range 29-71). Among the 110 clinical trials, there was not enough information to establish use of randomization, comparator type, allocation, outcome, and number of patients to be enrolled for 38 (34.5%), 44 (40.0%), 62 (56.4%), 66 (60.0%), and 98 (89.1%), respectively. **The first step towards ensuring compliance of 505(o)(3) postmarketing studies or clinical trials is to make comprehensive information about these studies in approval documents or by other means publicly available**, including a clear study design (eg, animal trial, prospective cohort study), trial endpoints, potential comparator arms, study populations, follow-up duration, and a target sample size, as well as a ClinicalTrials.gov NCT number.

Insufficient information is available about 505(o)(3) postmarketing study and clinical trial status. To determine the status of these studies, we used the Postmarketing Study and Clinical Trial Requirements and Commitments Database File, which is publicly accessible through the FDA website and includes descriptions, schedules for completing, and characterizations of the current status of postmarketing requirements. Unfortunately, fulfilled and released requirements are only displayed on the online database for one year after the date of fulfillment or release, even if the studies were delayed in completion, precluding comprehensive tracking of these studies. Despite extensive searching of the FDA website and using Google, 131 (30.0%) postmarketing studies for drugs approved by the FDA between 2009 and 2012 did not have enough information in any publicly available source to determine a recent, up to date status. **The FDA should maintain and make publicly available a comprehensive database of postmarketing requirements that includes ClinicalTrials.gov NCT numbers, is updated quarterly and for which fulfilled and released postmarketing requirements are never removed from the database, so that studies can be more reliably tracked**.

Insufficient information is available about reasons for sponsor noncompliance with the milestones established for 505(o)(3) postmarketing study and clinical trials. When sponsors were noncompliant with milestones, including study delays or terminations, no publicly available information was available. The FDA should consider making certain components of their Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), a non-publicly available database that includes information for prescription drug postmarketing requirements, publicly available. In particular, it appears as if DARRTS includes annual status reports, which are the detailed reports that drug sponsors must submit each year to the FDA on the status of each open postmarketing requirement. **All annual status reports including explanations for sponsor noncompliance with milestones established for these postmarketing studies, including whether the FDA judged the explanation to be reasonable or non-reasonable, should be made public.**

Timely completion and public results reporting of 505(o)(3) postmarketing studies and clinical trials needs to be prioritized. In our study, there were 50 prospective cohort studies, registries, and clinical trials classified as completed or terminated on ClinicalTrials.gov; 36 (72.0%) had reported results, while 14 (28.0%) had not reported any results. Among those that reported results (either on ClinicalTrials.gov or in a publication), the median time from FDA approval to results reporting was 47 months (interquartile range 32-67). Although one third of postmarket studies (15/47 (31.9%)) reported public results ahead of schedule (median 19 (10-23) months before the FDA report submission deadline), two thirds (32/47 (68.1%)) reported results behind schedule (14 (7-14) months after the deadline).

Approximately half (69 (51.5%)) of all 134 required prospective cohort studies, registries, or clinical trials reported results on ClinicalTrials.gov or were published.

These findings are consistent with a cross-sectional analysis evaluating the timeliness of postmarketing requirements for 135 new drugs and biologics approved by the FDA between January 2013 and December 2016 (JAMA Intern Med 2022;182(11):1223-1226. Available at: https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2797103). The investigators identified 387 PMRs and 87 reportable PMCs associated with these approvals, 330 (69.6%) of which were expected to be completed by Q4-2020, including 282 submitted or fulfilled and 48 due but not completed. Of the 330 to be completed by Q4-2020, 238 (72.1%) were late, including 190 that were completed by Q4-2020. Specifically, for 181 requirements under the FDA Amendments Act, 129 (71.3%) were late. Several other studies, including GAO reports, have also found that postmarketing studies are frequently delayed or incomplete (Drug Saf 2022;45(4):305-318. Available at: https://link.springer.com/article/10.1007/s40264-022-01152-9). Therefore, **all efforts should be made to ensure that 505(o)(3) postmarketing studies and clinical trials are completed in a timely manner, in accordance with the agreed upon milestones, and that the results are promptly made publicly available through ClinicalTrials.gov, as well as the FDA's revised assessment of drug safety.**

Again, we appreciate the opportunity to comment on this FDA draft guidance for industry. We hope that our suggestions might strengthen the FDA's program for sponsors of human prescription drugs required to conduct postmarketing studies or clinical trials under section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act.

Best Regards,

Reshma Ramachandran, MD, MHS, MPP
Assistant Professor of Medicine
Yale University

Joshua D. Wallach, PhD
Assistant Professor of Epidemiology
Rollins School of Public Health, Emory University

Joseph S. Ross, MD, MHS
Professor of Medicine and Public Health
Yale University