June 24, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-N-0093: Interim Assessment of the Program for Enhanced Review Transparency and Communication; Public Meeting and Establishment of Docket; 80 FR 22532 (April 22, 2015)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) and Biotechnology Industry Organization (BIO) submit these comments in response to the Federal Register notice entitled "Interim Assessment of the Program for Enhanced Review Transparency and Communication; Public Meeting and Establishment of Docket"[1] issued by the U.S. Food and Drug Administration (FDA).

PhRMA represents the country's leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than $600 billion in the search for new treatments and cures, including an estimated $51.2 billion in 2014 alone.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

I. GENERAL COMMENTS

FDA and biopharmaceutical companies agreed to establish the Program for Enhanced Review Transparency and Communication for New Molecular Entity New Drug Applications (NME NDAs) and Original Biologics License Applications (BLAs) (hereafter referred to as "the NME Review Program" or "the Program") under PDUFA V with the goal "to improve the efficiency

[1] 80 Fed. Reg. 22532 (April 22, 2015).

and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval, ensuring that patients have timely access to safe, effective, and high quality new drugs and biologics."[2]

The NME Review Program is built on a foundation of effective two-way communication throughout the drug development and regulatory review process. The Program is intended to promote greater regulatory transparency and predictability, resulting in improved efficiency and effectiveness during the first cycle of review. An efficient and effective review process that allows for timely responses to FDA questions and information for sponsors can help ensure timely patient access to safe, effective, and high-quality new drugs and biologics.

To date, based on the data available from FY2013 – FY2014, the Program appears to be accomplishing its goal of increasing the likelihood of first-cycle approval for NME NDA and original BLA applications.[3] The interim assessment of the Program found that first-cycle approval rates in the Program were statistically significantly higher than in the baseline prior to PDUFA V.[4] The overall first-cycle approval rate in the Program is almost 72%, with the first-cycle approval rate for Priority applications often exceeding 90%.[5]

To assist FDA with its efforts to evaluate the performance of the Program to date, PhRMA and BIO submit the following comments.

II. SPECIFIC COMMENTS

In addition to the general comments above, PhRMA and BIO would like to recommend specific comments as outlined below.

1. PhRMA and BIO PDUFA Tracking Database

PhRMA and BIO follow member companies' experience with the NME Review Program through a collection of data on NME NDA and original BLA applications from member companies through the PhRMA and BIO PDUFA Tracking Database (hereafter referred to as "the Database").

Data from the PhRMA and BIO Database regarding the FDA performance during the first two years of the Program appear to be generally consistent with findings of the independent interim

[2] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 (the "PDUFA V Goals Letter"), Section II.B.
[3] *See* "Assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs in PDUFA V," Interim Report for FY 2013-2014 by Eastern Research Group, March 27, 2015, available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM436448.pdf
[4] *Id.*
[5] *Id.*

assessment of the Program by the Eastern Research Group, Inc. (ERG) and support the interim conclusion that, to date, the Program has been effective in increasing the likelihood of first-cycle approvals for NME applications.

2. Pre-submission Meeting and Filing Period

PhRMA and BIO member companies agree with the ERG report finding that Application Orientation Meetings help establish early communication between applicants and FDA about review expectations and perspectives leading to better outcomes. Consistent with the ERG recommendation, BIO and PhRMA would encourage the Agency to consider consistent adoption of discretional Application Orientation Meetings across FDA review divisions, particularly for expedited Priority review applications and Breakthrough Therapy applications.[6]

BIO and PhRMA agree with the report findings that communication during the IND stage overall appears to be useful in guiding sponsors in development of study designs, establish active communication channels with sponsors before application submission, and gain familiarity with data that will be included in future NDA/BLAs.[7]

3. Mid-Cycle and Other Review Communications

Biopharmaceutical companies agree with the ERG recommendation that it would be helpful for FDA to adopt good communication practices around information requests and amendments to help ensure a more predictable and efficient review process.[8]

Companies appreciate FDA's efforts to implement a number of good practices in real-time, and not wait until the final evaluation of the Program, such as providing applicants with early notice of mid-cycle communication topics, and allowing two-way communication to ask clarifying questions.[9] BIO and PhRMA note the ERG report finding that mid-cycle communications "have generally been most efficient and least burdensome to review teams when attendees are selected based on anticipated need rather than including the entire FDA team."[10] Companies agree with the report recommendation that participation in mid-cycle communications should be focused on core team members and disciplines with issues[11] and encourages the Agency to consistently implement these internal guidelines.

[6] *See* the Interim Report, Specific interim findings and recommendations, S2.
[7] *See* the Interim Report, Sec. 3.2 at p. 23.
[8] *See* the Interim Report, Specific interim findings and recommendations S3.
[9] *Id.,* S5.
[10] *Id.,* S6.
[11] *Id.*

4. Discipline Review Letters and Late-Cycle Meeting

BIO and PhRMA note that, consistent with the ERG interim report and the PhRMA and BIO database analyses, FDA rarely issued Discipline Review (DR) Letters to applicants in the Program.[12] Only 15.6% of program applications received a DR letter(s) according to the ERG report. The PDUFA V Goals Letter specifies that since the NME Program application is expected to be complete at time of submission, FDA intends to complete primary and secondary discipline reviews of the application and issue DR letters in advance of the planned late-cycle meeting or include in late-cycle briefing package.[13] PhRMA and BIO member companies would like to reiterate the value of the DR Letters and encourages FDA to issue DR Letters prior to the Program's late-cycle meetings to facilitate timely communication of potential issues as identified by discipline's review.

Biopharmaceutical companies agree with the ERG report finding that late-cycle meetings were particularly helpful when there were significant issues to discuss that could be resolved in the first review cycle. In addition, late-cycle meetings provided an opportunity for FDA and applicants to discuss labeling and post-marketing commitments and requirements. Companies agree with the ERG finding and recommendation that providing explanations/rationale for proposed label changes helped both FDA and applicants to communicate effectively and allowed for timely completion of labeling discussions. BIO and PhRMA support the recommendation that FDA adopt inclusion of explanations/rationale for proposed labeling changes as a good practice.[14] Further, BIO and PhRMA believe that more explicit discussion of the research questions that should be addressed in the post-marketing setting would be helpful to have occur during the LCM.

BIO and PhRMA also agree with the ERG finding and recommendation that early involvement of the signatory authority can help ensure timely feedback and resolution of any issues identified by the FDA review team and can foster early agreement, thereby facilitating timely labeling decisions and avoiding last-minute surprises if the Office identifies concerns that the review division did not.[15] We encourage FDA to institute policies and procedures to ensure that such senior level engagement occurs consistently at the late-cycle meetings, followed by timely management input into the content of the labeling.

Moreover, final labeling discussions between FDA and companies continue to extend very late into the review process (sometimes right up to the PDUFA deadline), decreasing the opportunity for meaningful dialog about the labeling. We encourage FDA to consider methods for beginning such discussions earlier in the review cycle.

[12] *See* the Interim Report, Sec. 3.5.
[13] *See* the PDUFA V Goals Letter, Section II.A.6.
[14] *See* the Interim Report, Specific interim findings and recommendations, S7.
[15] *Id.*, S4.

5. PDUFA Goal Extensions and Major Amendments

According to the ERG report, 18.8% of applications in the Program received a goal extension of 3 months due to a major amendment,[16] with approximately half of these extensions issued for Priority applications.[17] The ERG report states that "program applications with a major amendment were also correlated with a higher first-cycle approval rate than those without a major amendment. This finding aligns with the expectation that extending the goal date to review a major amendment should lead to approval in the first cycle rather than requiring resubmission and a second cycle of review."[18] Based on PhRMA and BIO member companies' data, major amendments for Program applications were solicited by FDA, often very close to the original review goal date. Considering that Program applications must be complete at the time of submission as agreed by a sponsor and FDA and considering increased Program communications intended to identify and resolve issues early in the review process, BIO and PhRMA would like to better understand the Agency's rationale for qualifying information requests as major amendments and what could be done to avoid major amendments – especially very close to the PDUFA goal date.

6. Inspections

Biopharmaceutical companies agree with the ERG report finding that inconsistent availability and communication of information about the status and results of inspections has hindered review transparency and predictability.[19] BIO and PhRMA support the recommendation that FDA should examine the process for disseminating information about inspections and encourages the Agency to improve internal communication of inspection information between relevant Offices, review divisions, and applicants. Further, consideration should be given to the extensive information requests issued to companies by the Office of Scientific Investigation. This request is designed to facilitate the timely selection of inspection sites. However, this request is extensive, resource intensive to retrieve, and often redundant with previously submitted data, and it is unclear how this information is used by FDA. BIO and PhRMA would like to better understand the Agency's rationale for the Office of Scientific Investigation's information requests, given the extensive amounts of resources required to retrieve, report, and store this information. We hope that the establishment of FDA's new Office of Pharmaceutical Quality will improve the process for scheduling inspections and reporting inspectional findings, and we suggest that the final ERG report assesses the impact of the reorganization on the inspections process.

[16] *See* the Interim Report, Sec. 3.8, Goal Extensions at p. 44.
[17] PhRMA and BIO PDUFA Tracking Database analyses.
[18] *Id*.
[19] *See* the Interim Report, Specific interim findings and recommendations, S8.

7. Program Resources

PhRMA and BIO member companies note the ERG report's statement that FDA reviewers felt that the Program implementation has not been resource-neutral and increased the burden on FDA's primary reviewers.[20] However, review teams have been able to manage this burden. BIO and PhRMA note that the review timelines for Program applications were extended by 2 months under PDUFA V to help FDA reviewers meet review performance goals and accommodate workload associated with the additional meetings. We acknowledge the dedication of the FDA staff to meet these goals despite the hiring challenges that the Agency has faced in recent years. BIO and PhRMA look forward to continue discussions with FDA to better understand the Agency's resource needs for the Program, including any data supporting the ERG report's statements about resources for the Program.

III. CONCLUSION

PhRMA and BIO appreciate the Agency's efforts to meet the NME Review Program's goals as outlined in the PDUFA V Goals Letter. PhRMA and BIO appreciate the opportunity to share our thoughts on the performance of the Program to date and we look forward to continue working with all stakeholders as the Agency continues to implement the NME Review Program.

Respectfully submitted,

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[20] *Id*., O4.