March 27, 2017

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2015-D-2537: Submission of Quality Metrics Data; Revised Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's Revised Draft Guidance for Industry *Submission of Quality Metrics Data* (Revised Draft Guidance).

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.

BIO thanks the FDA for revising and publishing for public stakeholder input a Revised Draft Guidance regarding quality metrics. It is clear from this revised document that FDA has seriously considered the feedback on the initial 2015 Draft Guidance for Industry *Request for Quality Metrics*.[1] We appreciate the inclusion in the Revised Draft Guidance of Appendix B: Examples to provide companies additional guidance regarding each of the metrics FDA will be calculating.

We would like to reiterate that in general, BIO is supportive of FDA's effort to modernize regulatory oversight of drug quality and promotion of post-approval improvements. We believe metrics, when contextualized, tested, and appropriately defined, have the potential to provide a valuable tool to quantify product quality. However, we reiterate that any metrics collection must have the appropriate benefit/burden balance for both the Agency and industry.

It is important to ensure that the terminology used is well-defined and as specific as possible. The effort taken to prepare these metrics should be commensurate with the value they provide in establishing or predicting the quality status of a manufacturing site or product. We believe that open dialogue between FDA and industry will be a key factor in the success of this program. BIO members are committed to manufacturing high-quality

[1] BIO Comments on FDA Draft Guidance *Request for Quality Metrics* (November 2015) https://www.bio.org/advocacy/letters/quality-metrics-bio-comments-fda-draft-guidance-request-quality-metrics

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

products for patients and fully support the underlying goals of this program. We offer the below suggestions to ensure the success of this initiative for all stakeholders.

A. Implementation

BIO acknowledges that as this is an initial voluntary phase, it is likely that the companies that choose to participate will be the ones that have systems already in place that will allow submission of the requested metrics data. However, if FDA intends to open the electronic portal in January 2018 and expects to publish the notice with instructions and dates no fewer than 30 days prior to opening, time is short on finalizing the processes companies need to follow and what exact information will need to be collected. Companies likely need to be preparing now to submit data in 2018. This becomes a greater concern if FDA decides that changes need to be made to the Revised Draft Guidance based on the solicited public feedback. Therefore, we ask FDA to publish this Federal Register notice as soon as possible, especially if it contains any changes to the current understanding of the program, so that companies can make all necessary changes before the voluntary reporting period begins. We also believe that the issuance of a Final Guidance before beginning the voluntary program would be beneficial for both the Agency and industry as stakeholders would be certain about what information FDA is seeking to obtain and be more confident that they are providing what will be of most use to FDA. This will help in ensure the success of the voluntary phase and will aid in the analysis and evaluation.

The Federal Register Notice and Revised Draft Guidance discuss that FDA expects to encourage reporting where the data is segmented on a quarterly basis throughout a single calendar year and to begin collecting data in January 2018. BIO and its members initially understood this to mean that submission of the requested quality data would be prospective and not retrospective (e.g., that submitted data would be 2018 data, not 2017 data). We are now aware of additional information provided by FDA at recent meetings (such as the 2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference held in February) that the collection will be of 2017 data and that the collection period will be just three months, from January through March of 2018. In light of this additional information, we reiterate the importance of publishing the Federal Register Notice with final details for this program as early as possible, and potentially pushing the start of the collection period later into 2018. As mentioned previously, companies that wish to participate in the voluntary program would need to be ensuring their systems and internal processes are collecting the appropriate information now. Any changes made to the proposed program between now and the publication of the Federal Register Notice will cause companies to need to reassess, possibly change their systems, and verify their ongoing data collection as well as data already collected. Further, we would recommend that FDA extend the collection period from three months to at least six. The electronic portal and submission of the metrics data will be unfamiliar to all involved and allowing more time for submission will ensure companies can verify their data and ensure the data provided aligns with FDA's expectations. This will also allow for additional time for troubleshooting should the electronic portal or submission not be working as expected.

We appreciate that FDA does not intend to take enforcement action based on errors in a submission as part of the voluntary phase provided the submission is made in good faith. It is important that before enforcement is based on the calculation of these quality metrics,

even in conjunction with other information, that all Stakeholders agree on and fully understand the definitions and the correlation between the metrics and actual product quality.

BIO notes that because of the complexity of product quality and any quality metrics program, it is likely that after this initial voluntary phase, further iterations of the program will need to be tested before FDA moves to full reliance on quality metrics as a part of a risk-based assessment. This may involve further voluntary or pilot programs to ensure that the metrics are answering the appropriate questions, providing FDA and industry with useful information, and that the metrics correlate to product quality. We encourage robust public participation in this process, such as through additional pilots, phases, and public meetings. Further, FDA may consider phasing-in how it intends to use the data it receives and how this will play into any future risk-assessments. As we discuss further below, understanding the evaluation criteria and what success of the voluntary phase looks like will be critical to the program.

B. Assessment

While the Federal Register Notice states that "After evaluating the results of the voluntary phase of the quality metrics program in 2018, FDA intends to initiate notice and comment rulemaking under existing statutory authority to develop a mandatory quality metrics reporting program." there is no further detail regarding what this evaluation will entail. The Revised Draft Guidance is silent on this topic as well, only saying that FDA intends to publish an analysis of the data received to share what the Agency learned. It will be important for stakeholders to understand what success of the voluntary phase looks like to FDA as well as what the criteria are for moving on to structuring the mandatory program via notice and rulemaking. BIO is pleased to see that FDA intends to publish this analysis as transparency regarding this program will be important. However, it is unclear at this time how detailed this report will be; will it include high-level findings, or will it go into some amount of detail so that all stakeholders can understand how FDA arrived at its ultimate conclusion? We suggest that FDA incorporates as much public input during this assessment and publishes its analysis as possible in order to ensure all stakeholders have the opportunity to understand FDA's analysis and provide input before FDA moves forward. Public meetings and interactive dialogue sessions would be good ways to ensure this.

BIO appreciates that FDA intends to provide opportunities for those participating in the voluntary phase to provide feedback and additional comments as we believe that for a quality metrics program to be workable and successful, its set-up and testing will need to be through an iterative process, with open dialogue between FDA and industry being a key factor in its success. We believe it would be helpful for participants in the voluntary phase to be provided with information regarding their metrics and their performance relative to the whole body of metrics FDA calculates. It would also be beneficial if those that participate in the voluntary phase have the ability to discuss potential improvements to the program with FDA as they will have information and experiences working with the electronic portal and collection of metrics data that would be helpful to FDA as it moves forward. This input would allow FDA to understand, from the company perspective, how the collection of data and submission works, identify potential hurdles, stumbling blocks, or other areas of burden they may otherwise not see when just looking at the submitted data. In order for this

program to be successful the effort taken to prepare these metrics should be commensurate with the value they provide in establishing or predicting the quality status of a manufacturing site or product and actually give FDA a meaningful set of information they otherwise would not have.

While we understand that movement to notice and rulemaking of a mandatory program will be dependent on the outcome of the evaluation and analysis of the voluntary program, it would be helpful for stakeholders to understand FDA's general thinking on the timing of this notice and rulemaking. For instance, does FDA envision this to begin shortly after the analysis and evaluation of the voluntary program, 2 or more years after, etc? Additionally, if the evaluation determines that there are still many variables and details to work out before moving to a mandatory program would be feasible, does FDA intend to revise its thinking and start additional phases of the program? The answers to these questions are important for stakeholders to understand.

C. Confidentiality of Data

BIO is supportive of FDA's stated position that it does not intend to publically disclose information submitted to the Agency as part of the voluntary phase of the quality metrics program that is exempt form disclosure under the Freedom of Information Act (FOIA) (lines 541-544). BIO believes that FDA should not release metrics to the public and all submitted data should be kept confidential. The context and understanding of metrics among organizations, products, and various types of operations is complex. It is very likely that release of such information would lead to misinterpretation and confusion, in turn resulting in inappropriate actions by physicians, patients, and supply chain partners.

It is still our belief that in any Final Guidance, FDA should clearly state the basis under FOIA and FDA regulations for ensuring that FDA's intent not to permit disclosure of quality metric data submissions will, in fact, be implemented. Quality metric data submissions would clearly fall under the FOIA exemption from disclosure for trade secrets and confidential commercial or financial information.[2] Indeed, that exemption was specifically framed to encourage submitters to voluntarily furnish useful information of this type to the government.[3] As defined in FDA regulations, a trade secret may consist of "any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort" and "[t]here must be a direct relationship between the trade secret and the productive process."[4] "Commercial or financial information that is privileged or confidential" applies to "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs."[5] Information that would be submitted under FDA's quality metrics program clearly meets these standards. Such information would customarily not be released to the public,

[2] 5 U.S.C. § 552(b)(4).
[3] See *Critical Mass Energy Project v NRC*, 975 F.2d 871, 878 (D.C. 1992) (*en banc*).
[4] 21 C.F.R. §20.61(a).
[5] 21 C.F.R. §20.61(b).

and could, if disclosed, cause substantial harm to the competitive position of the submitter and impair FDA's ability to obtain reliable information in the future.

D. Reporting for Certain Covered Establishments

As BIO believes that the application holder should report the requested data to FDA, not the CMO, we appreciate that in the Revised Draft Guidance, FDA states its preference for all covered establishments to work with a product reporting establishment so that each product reporting establishment submits a single product report (lines 159-161). However, we note that FDA still gives the option of covered establishments to send site reports directly to FDA. BIO would like to note that supply chains for a given product may be quite complex with different manufacturers, packagers and laboratories used. The application holder is generally the sole entity with full view into the issues associated with a contracted product.

E. Quality Metrics FDA Intends to Calculate

Invalidated Out-of-Specification (OOS) Rate (IOOSR)

FDA has indicated that two metrics are to be calculated for invalidated OOS per superscript 29, however Appendix A.6 sums the release and stability results. For clarity, we ask FDA to clarify the reporting requirements for OOS in the appendices as locations exist only for the sum of lot release and stability tests and not these test types individually.

F. Quality Metrics Data that May be Reported

While BIO appreciates that the FDA has reduced the number of quality metrics that FDA intends to calculate (three in the Revised Draft Guidance as compared to the original four, and the deletion of the voluntary metrics), we do note that this comes with an increase in the number of quality metrics data that participating companies will need to report (eleven as compared to the original ten).

It would also be helpful for FDA to clarify the mechanism for correcting submitted metrics as this will be an important component of the program for companies to understand.

G. Quality Metrics Reporters List

BIO understands FDA's intention to publish a Reporter's List including the names of establishments that are participating in the voluntary phase. However, we believe that the List as proposed in the Revised Draft Guidance is premature, particularly the proposal to stratify participating companies into various categories based on the type and amount of data provided. While it is true that this type of information may be helpful to third parties, it is currently unclear and unproven that the quality metrics FDA intends to calculate correlate to actual product quality in a meaningful way.

We understand that FDA makes clear in the Revised Draft Guidance that the List is simply whether an establishment submitted data and how much and is not an indication of FDA's evaluation of the submitted data. However, by publically ranking establishments, FDA effectively creates the impression that FDA favors or endorses a private sector establishment and that establishment's activities, products, and services over other establishments. This potentially creates an unfair advantage to establishments that have simplified supply chains because they could more easily be ranked as a "Top Tier" company. In contrast, establishments with complex supply chains would publically be viewed as being of a "lower tier". Prior to making public any such a list, industry and FDA should further discuss alternative approaches to encouraging participation in the program.

Should FDA move forward with the Reporter's List, BIO suggests it be a simple list of those participating in the voluntary phase, with no category differentiation. There are many reasons that a company may decide not to participate in the voluntary phase of this program that do not have to do with product quality. Such companies should not be punished or be perceived as having lower quality products due to these business decisions, especially in this voluntary phase.

H. Text Comments

BIO is pleased to see that FDA has heard the feedback from stakeholders that the ability to provide text comments when submitting metrics data will be helpful to provide explanation of submitted data. It would be helpful for FDA to clarify whether there will be one 300-word text comment available for the entire data submission, or if there will be one 300-word text comment available for each metrics data collected.

I. Conclusion

BIO appreciates this opportunity to submit comments on FDA's Revised Draft Guidance for Industry *Submission of Quality Metrics Data*. We would like to reiterate our support for the underlying goals of the quality metrics initiative and to offer our assistance as FDA and industry begin the submission and analysis of metrics. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Cartier Esham, Ph.D.
Executive Vice President, Emerging Companies Section &
Vice President, Science & Regulatory Affairs
Biotechnology Innovation Organization