Biotechnology Industry Organization

November 24, 2015

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

Re: Docket No. FDA-2015-D-2537: Draft Guidance for Industry Request for Quality Metrics

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance entitled "Request for Quality Metrics" (Draft Guidance).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.

In general, BIO is supportive of FDA's effort to modernize regulatory oversight of drug quality and promotion of post-approval improvements, and of FDA's quality metrics initiative overall. Assessing across organizations, programs, products, and processes can be a considerable challenge, and many factors, including where a particular product is in its lifecycle, may influence some measures. As a result, BIO is supportive of FDA's intent to use the quality metrics gathered as a tool and in context with other sources of quality data and not as the sole way for FDA to determine the state of quality within sites or products. It would be helpful for FDA to more clearly state the intended use of the collected metrics and the benefits to industry. We understand that regulatory relief (*e.g.*, less frequent inspections, post-approval manufacturing change categories) may be granted based on positive high-quality metrics; however, it is unclear whether FDA would use low-quality metrics as an indicator to increase inspections at a particular entity. We believe metrics can provide a valuable tool to quantify product quality and can assist the Agency in developing a risk-based inspection program. It will be important to view these metrics in their proper context and in the broader set of information and knowledge FDA possesses. BIO recommends that FDA clarify that the quality metrics data will be used as an input to the risk-based inspection model and for surveillance purposes only; FDA will not take compliance actions solely based on quality metrics data evaluation. In addition, BIO requests that clarity be provided regarding the extent to which CBER will implement this new approach for facilities it inspects.

We recognize that the FDA is requesting reporting of data and that the calculation of the metrics will be performed by FDA. It would be helpful if the Agency were to define the calculations that they envision performing with the reported data and any weighting they may envisage in establishing the overall risk quotient from this information.

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Of significant importance is establishing a small number of key metrics that are clearly defined and generated in a consistent manner. It is also 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. BIO sees this initiative as a journey and this Draft Guidance as a first step. We note that it will likely take several iterations to arrive at metrics and definitions that provide optimal value as well as to ensure the collection and submission of the quality data points are efficient. Additionally, as this program and its metrics collection may be substantially different from current practice, it will likely take covered establishments additional time, iterations, and resources to be able to complete these activities. 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 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. Assessment Period

As stated in our introductory remarks above, BIO believes that this Draft Guidance is a first step in an iterative process between FDA and industry to ensure that: (1) definitions are clear and applicable across manufacturing type; (2) the metrics are appropriate for the stated goals; and (3) the collection, submission, and analysis of the metrics data are not unduly burdensome to industry or FDA. To this end, BIO encourages FDA to implement a two-year assessment period where data are collected from industry and FDA can have a dialogue with stakeholders prior to putting the metric data into the Inspections Risk Model officially. This will allow stakeholders to coalesce around a set of metrics and definitions that will provide optimal value to FDA. An assessment period will also allow FDA and industry to identify any unintended consequences that may arise from the collection of these metrics. For example, the optional metric of CAPA effectiveness, as currently written, may drive down employee retraining rates but still miss the mark in appropriately addressing root cause. Additionally, many international regulatory agencies rely on inspections from FDA for entities that are in the United States. As such, any change in the FDA inspection schedule could impact international regulatory action. This may be remedied by providing documentation citing an entity's regulatory relief from FDA that can be given to the foreign regulatory agency to satisfy their requirement.

We suggest that FDA start with a small number of well-defined metrics and work in an iterative process to ensure the validity of these definitions and metrics. BIO believes that the current number of proposed metrics is adequate, with some modifications as described below. We note that whichever metrics are ultimately chosen, the metrics need to give a meaningful picture of what is happening within manufacturing sites, across the landscape of products manufactured. It will be important for FDA to balance the need to collect and calculate this data to obtain a true picture of the quality of products and sites with ensuring data quality/integrity and the burden on both industry and the Agency of this activity. As mentioned above, 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. The burden should be evaluated as part of the initial two-year assessment period.

As we discuss in more detail below, in order to reduce the upfront burden at the start of the collection period, it may be beneficial to allow entities to report by site segmented by product while systems are being implemented and updated, and to allow for a transition to reporting by product segmented by site at a named future date. Additionally, allowing the timing of the submission of metrics to be aligned with the firm's internal annual product review (APR) schedule would also help to reduce burden on industry.

We recommend that these metrics be implemented no sooner than six months after the date of finalization of the Guidance. A minimum of six month grace period between the date of Guidance finalization and implementation would allow manufacturers time to build or modify quality systems to acquire more robust data for reporting on these metrics, thereby improving compliance with regulatory reporting requirements set forth in the Guidance. We further urge the Agency to consider requests for data within the scope of this Guidance to be prospective rather than retrospective. For example, if the Guidance is finalized in 2016, we ask the Agency to consider data request from this date forward, allowing for an implementation buffer, recognizing the necessity for establishments to build systems to support such requests.

As part of a continuous improvement approach to inspection planning and prioritization, we also encourage FDA to allow for the refinement of these metrics and data points over time after the assessment period.

B. Transparency

In order to use quality metrics for risk-based inspection scheduling and determination of post-approval manufacturing changes reporting category, transparency and communication between FDA and covered establishments will be crucial. It is important that stakeholders understand how they will be informed of any regulatory relief they are granted as a result of this program. We encourage FDA to work on defining a communication plan during the recommended assessment period to ensure it meets the needs of both FDA and covered establishments. It would also be useful to have more detail surrounding how FDA will be using the metrics to make risk-based inspectional decisions and how poor quality metric performance could influence regulatory action. We recommend that manufacturers be informed – upon request and confidentially – where they fall within their peer group. It will additionally be helpful for FDA to inform companies how peer groups are defined (*e.g.*, company size, number of products, type of products, etc.). Entities can then track their progress internally and in relation to similar categories of establishments over time.

C. Confidentiality of Data

BIO is supportive of FDA's stated position that it will not publicly disclose quality metric data submissions (lines 310-311). 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.

In any Final Guidance, FDA should clearly state the basis under the Freedom of Information Act (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. [1] Indeed, that exemption was specifically framed to encourage submitters to voluntarily furnish useful information of this type to the government. [2] 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." [3] "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." [4] 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, 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. Technical Details and Corrections

BIO is supportive of FDA's mention of additional technical details in a separate technical specification (lines 582-583) as described in the Draft Guidance. We also are encouraged that, as noted in the Public Meeting on August 24th, the Technical Conformance Guide and Technical Specification will be available for public comment. We support FDA's intent to publish these documents for public review and comment so that entities will have a clearer picture of how reporting will work.

To this end, it is currently unclear how an entity would handle any corrections that need to be made to data submitted to FDA. Reporting timeframes may not be the same for all metrics, and not all metrics may be best represented by data reported on a quarterly basis as currently requested. It is possible that a data point may be identified in one quarter and confirmed or disproven in the next (*e.g.*, invalidated out-of-specification (OOS) rate) or that other corrections will need to be made after submission. In the currently proposed system of reporting annually segmented by quarter, it is unclear how this correction would be reported. Clear definitions should be provided to address which data should be included for

[1] 5 U.S.C. § 552(b)(4).
[2] See *Critical Mass Energy Project v NRC*, 975 F.2d 871, 878 (D.C. 1992) (*en banc*).
[3] 21 C.F.R. §20.61(a).
[4] 21 C.F.R. §20.61(b).

a given timeframe. Furthermore, other issues will likely be identified when entities begin reporting quality data to FDA. We believe this supports the importance of this program being an iterative process as well as the importance of the assessment period. For example, definitions should be provided to manage expectations, potentially align a manufacturer's process with Agency reporting expectations, and clarify the expected time frame for data reporting and submission to the Agency. Not only may definitions need to be adjusted, but questions and issues are likely to arise with the logistics of executing the program.

E. Reporting for Certain Covered Establishments

It is somewhat unclear based on the "Who reports for covered establishments" section for products manufactured by contract manufacturing organizations (CMOs), if the marketing application holder will be expected to obtain and report metrics from the relevant CMOs. Ultimately, BIO believes that the application holder should report the requested data to FDA, not the CMO. 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.

One possible consequence that may occur if the application holder does not submit the information is that CMO interpretation for the definitions of the quality data are not aligned with the application holder interpretation, leading to inconsistent data. Additionally, ambiguous reporting responsibility could lead to time-consuming haggling over supply/quality agreements to determine which party will submit the data to the FDA and to ensure the application holder's access to the data. There would likely be a lag time between collection of the data and submission to FDA as the application holder would likely request approval of data prior to its submission to FDA. For all of these reasons, BIO recommends that FDA make it explicitly clear that CMOs are expected to provide the appropriate data to the application holder, who, in turn, will be responsible for submitting this site data to the FDA.

F. Quality Metrics FDA Intends to Calculate

We reiterate the importance of clear, well-defined definitions that are applicable across product types and provide the most value while avoiding undue burden for both FDA and industry. Additionally, as acknowledged above, definitions will likely need refining over time and we envision an iterative process in which these changes can be made and tested. In general, trending of metrics may be helpful in order to look at how a given metric is performing over time. We offer specific comments on each of the four metrics FDA is currently proposing below.

I. Lot Acceptance Rate

BIO generally supports this metric as an indicator for product quality. We suggest that pending lots be excluded from this metric as pending lots relate to a lead-time issue and not necessarily a quality issue. This is especially true for biologic products which we discuss in more detail below. We also suggest that the metric should be "quality-related

rejected lots" not "specification-related rejected lots" as proposed in the Draft Guidance. Other reasons exist for rejection besides failing specifications. BIO believes "quality" is a more encompassing term to determine overall failed lots due to various quality reasons. One such reason is a "quality related reject," which is associated with a nonconformance or deviation resulting in concerns on quality and safety of the product leading to the rejection of the batch. A definition should be added for this term. Finally, regarding the definition of "lot attempted", we note that it is unclear from the definition when a lot is started, particularly from a biologics perspective. In addition, it is unclear what constitutes the end of a lot, particularly related to intermediates and packaging operations.

As such, we recommend the metric definition be edited to read:

> "1-x (x=the number of quality-related ~~specification-related~~ rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe)."

II. Product Quality Complaint Rate

BIO is supportive of using "product quality complaints received." Trying to further define complaint rates by "critical" or "confirmed" may be quite difficult and could lead to skewed reported data. We do recommend that the denominator of this metric be the total number of units distributed, not the total number of lots released. We believe that units distributed gives a better overall picture for this definition as there may be variability in the number of units produced per lot.

As such, we recommend the metric definition be edited to read:

> "the number of product quality complaints received for the product divided by the total number of units distributed ~~lots of the product released~~ in the same timeframe."

Complaints received in a given period are typically not representative of lots released in that timeframe. Due to intrinsic delay for released lots to enter the marketplace and eventual distribution to patients/consumers, complaints received are more commonly associated with lots released during the previous reporting period. Furthermore, an examination of the distributed units may provide additional quality information to "complaints per lot," since unit size is also dependent upon the reported defect from the complainant. For example, if the packaging configuration for a lot is 100 25X50mL (100 packages containing 25 vials, 50 mL each), the denominator for a reported defect associated with outer packaging is 100 units, whereas the denominator for a reported defect associated with the product itself (*e.g.*, appearance, product contact component, unit label) is 2500 units, which will impact the calculated complaint rate. This recommendation would more appropriately and accurately represent the product quality as measured by complaint rate. We recommend using distributed units as the basis for this metric because complaints received over a standardized unit of measure (*e.g.*, parts per million (PPM)) would allow for a more accurate reflection of increasing or decreasing complaint rates while minimizing the potential to mask actual data signals.

We also note that because of the variability in the number of units produced per lot between sites and between companies, an analysis of the data between similar product types will likely be unachievable. While we generally believe that trending may be helpful for all metrics being calculated, we think this is particularly true for complaint rates, especially for products that are made infrequently or have small lot sizes. In these cases, complaints may be few, but changes from the normal rate would be important to detect. Additionally, depending on the type of product, complaints may be seasonal (*e.g.*, allergy medications).

We also believe that consideration should be given as to how the metric will be determined in periods when no lots are produced yet complaints are received from lots produced in earlier periods, as there is a lag time between release and receipt of complaints.

Furthermore, it should be noted that as currently worded in the Draft Guidance, this metric can be interpreted to define complaints as inclusive of adverse events (AEs). We request the Agency limit the definition of "complaints received" to product quality complaints only, and not AEs. AE-related complaints are already submitted to, and captured in, the adverse event reporting database, and provided to the Agency.

Finally, it would be helpful to have further clarity regarding products with multiple concentrations and/or multiple presentations. BIO suggests reporting complaints based on final dosage form and not as one product as the latter may hide a problem with a particular presentation or concentration.

III. Invalidated out-of-specification (OOS) rate

BIO supports the concept of this metric as an indicator for laboratory performance; we note, however, that there are many points to consider when discussing this metric. A possible alternative might be to look at invalidated assays. We suggest that this metric only cover analytical data related to the specifications listed in the Certificate of Analysis (CoA). Further, as currently written, this metric can be calculated in more than one way:

[(# Invalidated OOS test result) ÷ (# OOS Test Results)] ÷ Total # Tests performed

or

(# Invalidated OOS test result) ÷ [(# OOS Test Results) ÷ (Total # Tests performed)]

BIO understands the former to be how the metric is intended to be calculated, but clarification is needed to ensure this definition is understood by all. Alternatively, this metric could be split into two metrics as follows:

1. # Invalidated OOS ÷ Total OOS
2. Total OOS ÷ Tests performed

We note that footnote 31 is specific to finished Drug Product (DP) only. Clarity is needed as to which parameters the Agency is seeking data specific to OOS, which should provide a more holistic picture of risk to product shortage at an earlier stage in the manufacturing process, and quality of an establishment/site when reviewing additional dosage forms such as formulated drug substance (DS). Only reviewing DP (finished product) results would limit the ability to appropriately assess and conclude on the quality metric.

IV. Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate

Should FDA choose to keep this metric, BIO recommends that the reporting deadline follow internal company timelines (*e.g.*, data reporting from an establishment based on the establishment due date to enable the establishment to meet global compliance for products that are distributed in more than one region/market) and ask FDA to refine the scope of this metric to account for new product approvals, as these may skew the data when calculating this metric, as an APR may not have occurred for a new product approval within the reporting timeframe. Furthermore, we request that the Agency consider how additional refinements to this metric could contribute to reporting of more transparent data across Industry, thereby reducing the Agency's burden in attempting to normalize data that could be represented or reported by various conflicting measures.

Additionally, FDA is requesting data from the annual due date of the product (line 552). However, the requested metric to be calculated (line 434) is based on the annual due date at the establishment. It is necessary to highlight that establishments may have procedural dates greater than 30 days.

G. Quality Data to be Reported

BIO appreciates that FDA has clearly listed what quality data is being requested in order to calculate the proposed quality metrics. We also appreciate that FDA acknowledges that for certain data it may not be possible, or may be difficult to differentiate between drugs manufactured for or in the United States versus all drugs manufactured, and that data may be reported for either, as long as it remains consistent. We offer the following specific comments on a few of the data points.

I. The number of lots rejected (line 535)

We suggest that FDA allow an establishment to submit numbers for each batch lot identified within their systems. Although each manufacturer would have different numbers, the information would be consistent within an establishment and aligned with the data being reviewed by the establishment during quality metric reviews. The request for number of lots rejected does not specify whether any data on process related controls (IPCs) not listed on a specification would be included or submitted. As an example, for monoclonal antibodies, unprocessed bulk testing is a critical IPC, but may not be listed on the drug substance disposition specification or CoA.

II. The number of lots attempted pending disposition for more than 30 days (line 538)

BIO understands that FDA is seeking to have metrics that are applicable across all types of products. As such, BIO recommends that this data point be revised as it is not relevant for certain types of biological products, or for certain products manufactured by CMOs. This metric, as currently defined, would require reporting of many in-process lots. For some product and process types, the normal cycle time may be significantly longer than 30 days and even as long as 120 days. Further, biologics often have long lead times for quality control (QC) testing and batch record review (*e.g.*, bioreactor batch records cannot be reviewed and closed until the bioreactor operations are terminated, typically several months for a perfusion based bioreactor). Drug substance and drug product lots for such products typically require more than 30 days from the last date of manufacturing to lot disposition and release of the lot, and the timing of release is not an indicator of a quality concern. For products manufactured by CMOs, the CMOs often establish timelines that require more than 30 days for release (*e.g.*, in some cases CMOs stipulate 6 weeks to send batch records to the marketing application holder for initial review). We recommend this definition be revised to be "pending disposition for more than 30 days due to quality related issues." We further recommend that FDA clarify that the pending disposition time-period commences at the time routine production and testing is completed so that the metric captures lots that sit with undetermined quality status due to quality investigations.

III. The number of OOS results for the product, including stability testing

BIO recommends that FDA clarify that this data point refers to long-term stability testing and does not include accelerated or intermediate International Conference on Harmonization (ICH) stability studies that may be conducted post-approval.

It is expected that accelerated/stressed stability conditions could generate expected OOS results. As new molecules and biological products are being characterized, or as new market opportunities are being realized for established molecules, accelerated/stressed stability conditions are often required. Requiring establishments to report OOS results for expected failures could give a false interpretation of a product's quality. Due to the inherent attributes of accelerated/stressed stability conditions, we urge the Agency to omit expected OOS results from this metric request.

IV. The number of invalidated OOS and OOS Result Definition (lines 544-545 and 700-704)

We request that the Agency expand the definition of OOS results to include the timing of or timeframe for OOS identification. As currently stated in the *Guidance for Industry on Investigating Out-of-Specification Test Results*, the analyst has the initial responsibility for ensuring accurate results and identifying errors that could result in invalid analyses. We further request that the Agency align this Quality Metrics Guidance with structure in

the OOS Test Results Guidance, and indicate that this identification is after the initial analyst review of the data.

H. Optional Metrics

BIO acknowledges that quality culture is an important factor for internal consideration. However, we note that assessing quality culture is difficult to do in a quantifiable, data-driven manner. When determining which metrics to use for risk-based inspection scheduling and other regulatory benefits as outlined for this program, it is important to keep in mind the end goal: assessing the quality of products and sites and the impact of these results to patients. We ask FDA to keep in mind the following points when assessing the proposed optional metrics as outlined in the Draft Guidance: is it meaningful to try to measure quality culture through these metrics, are these metrics objective, what do the results mean to patients, and are the products being manufactured better or worse as a result. We also suggest that FDA look at the possibility that some of these aspects of quality culture assessment may be better measured during inspections and could be part of the New Inspection Protocols Project (NIPP) with FDA sharing and engaging industry as this evolves.

A strong quality culture is important to achieve a reliable supply of quality product consistently. Quality culture needs to be linked to, and have a strong emphasis on, the patient. The understanding of quality culture vision, analysis, and measurement is still evolving and we encourage continued dialogue on this topic. In concept, BIO is supportive of the proposed process capability/performance metric as it is currently the only leading metric proposed and the most appropriate of the three optional metrics. We provide specific suggestions on this metric below.

We note that the overall discussion on quality culture and how it is measured is in the early stages. We recommend that FDA and industry continue the dialogue on quality culture and possible indicators, the outcomes of which could be reflected in future iterations of the program.

Additionally, while these metrics are being represented as optional, the Draft Guidance states that "data from these optional metrics may merit a reduction in inspection frequency" and FDA will consider "whether these metrics may provide a basis for FDA to use improved-risk based principles to determine the appropriate reporting category for post-approval manufacturing changes" (lines 441-447). We note that this implies that while these metrics are optional, it is in the best interest of entities to provide this information in order to take full advantage of the possible regulatory relief being offered. This may put entities with less familiarity or capacity for such quality metrics or entities that do not wish to provide these optional metrics for any reason at a disadvantage even if the quality of their sites and products is favorable. BIO believes that if FDA collects these metrics they should be optional.

BIO believes that, at this time, these optional metrics may not be ready for implementation in their current state. In the spirit of ongoing dialogue and improvement, we offer specific comments on each of the three proposed optional metrics below.

I. Senior Management Engagement

BIO acknowledges that senior management engagement is important to ensure quality culture throughout the organization; however, we suggest that there may be better ways to discover how involved senior management is than the proposed metric. As currently proposed, this metric is a binary question/answer that is attempting to glean information on a far more complex topic. Additionally, the metric does not necessarily imply there is a good quality culture at an establishment. It may be more meaningful to understand, possibly through discussion, about the APR/PQR process rather than just whether this is approved by senior management. We note that a more effective way for senior management to be engaged and foster a culture of quality is to actively participate cross-functionally in the APR or PQR review similar to a Management Review Meeting.

II. CAPA Effectiveness

BIO agrees that comprehensive corrective actions and preventive actions are important and may be a good indicator of a robust quality culture. We note, however, that CAPA effectiveness may be difficult to define and measure across the industry. In line with the overarching theme of clear definitions, the metric as currently described in the Draft Guidance allows for conflicting interpretations. As such, we request clarity on the nature of this metric to be site-based, not product-based. Additionally, this proposed metric focuses on a subset of deviation (human errors and retraining) and may result in the unintended consequence of driving down employee retraining rates when that may not appropriately address the root cause. In addition, there are several ways to interpret "lack of adequate training" without additional definition and clarification. For example, failure to follow procedure could be documented by one establishment as "lack of adequate training," and another as "human error." A holistic review of the CAPA system should be considered rather than a focused subset.

III. Process Capability/Performance

Identifying, monitoring, and controlling variation in the manufacturing process is important to assure high quality products. As such, BIO is supportive of this metric in concept as it is currently the only leading metric proposed and the most appropriate of the three optional metrics. However, we note that not all critical quality attributes (CQAs) lend themselves to statistical analysis. For example, CQAs are not all measured by numerical values (such as bioburden or sterility). Consequently, process capability and performance indices are not calculated for CQAs that are non-numeric. Therefore, a "Yes/No" value cannot adequately account for this proposed metric. For these non-numeric values, we propose an option of "NA" for not applicable, with an explanation (*e.g.*, that these values are addressed through the establishment's quality management system as there is no trending of non-numeric values). If the Agency is not amenable to this proposal, we request that the Guidance provide a more comprehensive method of determining an establishment's management's oversight of CQA as part of a product's APR/PQR. We fully support FDA's flexibility to allow sites to choose the process capability statistics (*e.g.,* CPK, PPK) that are used for this metric. We also note that this metric

may take more time to set up and implement for entities that do not currently have data collection systems in place that are already linked to the CAPA process.

We suggest the Agency rephrase the question in this metric reporting to determine whether the establishment has a process for performing these calculations once data exist for each CQA. In order to calculate meaningful process capability or performance index value(s), a minimum number of data points must exist for the process. If the data has not yet been generated for the CQA, then values might not exist for certain parameters, although they can be generated for other parameters in the same program. Therefore, it may not be possible to have a definitive "Yes/No" response to the question as currently stated. We propose rephrasing the language as follows:

> "Does the establishment have a process for calculating process capability or performance index for each CQA once sufficient data is available?"

We reiterate that the overall discussion on quality culture and how it is measured is in the early stages. We recommend that FDA and industry continue the dialogue on quality culture and possible indicators.

I. Additional Request for Comment

FDA has additionally asked for comment on three other aspects of the quality metrics program, we provide our feedback as follows.

I. Frequency of Quality Metrics Data Reporting

BIO agrees with the proposed submission frequency of annually, segmented by quarter. We reiterate that some clarity will be needed for corrections and other technical issues as highlighted above.

II. Reducing the Reporting Burden Based on Data Collection Timeframe

BIO is supportive of FDA's alternate timeframe for reporting to use the manufacturer's current timeframe for conducting its APRs or PQRs. This will be beneficial for both manufacturers and FDA. It will decrease the burden for reporting and will facilitate FDA's receipt of quality data in a more spread out manner as opposed to all at once. However, it should be acknowledged that with multiple products, there are multiple dates for these documents. Additionally, reporting data per site would not align with how the PQR data is captured and reviewed.

Another alternative proposal would be to allow a manufacturer to choose a date to align its submissions with what may be best internally. Once a company chooses the date, it would not be able to deviate from it. It may also be useful to know when FDA intends to run their inspection risk model to allow for manufacturers to choose a date that gives FDA the most up-to-date quality information available.

III. Including a Limited Text Field for Data Point/Metrics

BIO is supportive of including an optional text field that would allow entities to include explanations to provide contextual information about the data for each quality metric calculation. We suggest a 500 word "free-text" explanation to allow establishments to provide sufficient context and details regarding submitted metrics. We acknowledge that FDA would be unable to review all submitted comments (lines 638-639) but would expect this information would be reviewed if a signal were seen or if the calculated metric was problematic or unexpected in some way. This extra information could provide valuable data in such cases. Furthermore, we request that FDA provide feedback in the form of questions to the establishment if there are numbers that do not seem in line with historical performance or industry standard.

J. Conclusion

BIO appreciates this opportunity to comment on the Draft Guidance entitled "Request for Quality Metrics." 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 have included responses to the questions from the July 28 Federal Register Notice in the attached Appendix. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Victoria A. Dohnal, RAC
Manager, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Appendix-Responses to Questions in July 28 Federal Register Notice

1. *Are there other objective metrics that FDA should request in advance of or in lieu of an inspection that FDA should collect to improve our understanding of products and establishments for purposes of more informed, risk-based inspection scheduling and identification of potential product shortages?*

   It may be helpful to begin a dialog and explore metrics that may be predictive of potential drug shortages. This may be an appropriate optional metric for future consideration.

2. *Are the definitions of the metrics and associated data requests selected adequate and clear?*

   Please see our above comments on this topic for more detail. The product complaint metric would be more valuable if the number of product quality complaints received is divided by the number of units distributed rather than the total number of lots released. Because of the variability of the number of units produced per lot between sites and between companies, an analysis of the data between similar product types will be unachievable.

3. *Are the metrics requested from each business segment/type clear and appropriate*

   We refer FDA to our specific comments above and reiterate the need for clarity regarding CMOs to guard against over- or under-reporting. As there are complexities of interpretation and how to report for various establishments, we recommend FDA collate and provide Q&A's and reporting examples, particularly in the initial phase.

4. *Should the Agency explore collecting metrics from high-risk excipient producers, and if so, which excipients should be considered high-risk and what metrics should apply?*

   FDA should begin a dialogue to help define high risk excipient producers and determine which metrics would apply to these excipients and their producers.

5. *Should the Agency explore collecting metrics from the medical gas manufacturing industry?*

   FDA should discuss the possibility of including metrics from the medical gas manufacturing industry with those stakeholders.

6. *Should the Agency add the "Right First Time" metric (see section I.), and if so, should the definition be a rework/reprocessing rate or a measure of lots manufactured without processing deviations?*

   This metric is not ready for implementation but FDA should pursue a dialogue on the right first time metric; more information is needed before FDA can collect this metric and the definition must be fully understood by all stakeholders before it should move forward.

7. *What data standards/mechanisms would be useful to aid reporting and how should the submissions be structured?*

   As mentioned in our specific comments above, BIO looks forward to the release and public comment period of the Technical Conformance Guide and Technical Specification. It would be helpful if these documents include definitions of when data falls into scope (*e.g.*, standards in defining when something "counts" for the purposes of metrics reporting). In addition, we recommend the FDA provide further clarification of reporting for various types of supply chains, possibly through Q&A mentioned above. As evidenced by the comments on CMOs and text in the guidance related to US vs global market data there could be a lot of variability in the data received for meaningful analytics.

8. *Are there reporting hurdles to collecting metrics by reporting establishment/product (segmented by site) versus by site (segmented by product), and how can they be overcome?*

   There are reporting hurdles, as well as benefits, to reporting either by product (segmented by site) or by site (segmented by product). It currently seems that FDA is looking to use quality metrics data in two ways: to assess quality for inspections, which is focused more on the site; and to assess quality of drug product and possible drug shortages, which is focused more on the product. It is our understanding that FDA can calculate the proposed four quality metrics from data reported in either manner. We offer the following considerations for each reporting manner.

   <u>Product (segmented by site):</u> Having entities report in this manner gives the application holder final control over the data that is submitted. This gives better visibility to any possible quality issues for a product. The product is seen as a whole entity, as opposed to in scattered pieces. FDA also would not be getting different pieces of information from multiple places at potentially different times. The application holder would also see the full data set before it is sent to FDA and would be able to ensure consistent application of definitions. However, we note that this may entail more of an upfront burden for entities and it may take entities more time to be compliant as systems and agreements may need to be updated.

Site (segmented by product): Having entities report in this manner may reduce the upfront burden of quality data collection as this is more in line with current industry reporting practices. However, this may be challenging for CMOs to manage, the timing of submissions from multiple places would need to be synced to ensure compliance and that FDA receives all the relevant data at the same time, and may increase the chance of double reporting. This will also be increasing difficult as complexity is added reflecting all the different business relationships that currently exist between contract labs, contract manufacturers, and application holders. As applications holders outsource more pieces of the manufacturing of a drug, reporting by site segmented by product becomes increasingly complex and possibly difficult to manage from both the perspective of the manufacturer and FDA.

In order to reduce the upfront burden at the start of the collection period, it may be beneficial to allow entities to report by site segmented by product while systems are being implemented and updated and allow for a transition to reporting by product segmented by site at a named future date.

Alternatively, if the metrics can be accurately calculated regardless of the presentation for the data, it may be beneficial to allow application holders to choose which way to report their metrics as there are various business considerations that would need to be taken into account.

9. *FDA may consider whether to require the submission of quality metrics on a recurring basis. How frequently should metrics be reported and/or segmented within the reporting period (e.g., annually, semiannually, or quarterly)?*

   BIO agrees that submission of metrics annually segmented by quarter is the appropriate requirement for submission of quality metrics data.