PHARMA & BIOPHARMA
OUTSOURCING ASSOCIATION

Pharma & Biopharma Outsourcing Association
10 Alta Vista Dr.
Ringwood, NJ 07456
Tel: 201-788-7994
www.pharma-bio.org

To: Division of Dockets Management (HFA-305)

From: Pharma & Biopharma Outsourcing Association

Subject: Comments for Docket #: FDA-2015-D-2537:
Draft Guidance for Industry: Request for Quality Metrics

Date: November 25, 2015

The Pharma & Biopharma Outsourcing Association (PBOA), a trade association representing Contract Manufacturing Organizations and Contract Development & Manufacturing Organizations (collectively described as CDMOs for the purposes of this letter), appreciates the Food and Drug Administration's (FDA) efforts and goals to encourage continuous improvement within the pharmaceutical industry, and supports initiatives that possess potential benefits for industry, for patients, and for the FDA. To ensure that the maximum benefit of the proposed Quality Metrics initiative is achieved, with clear understanding of expectations by all parties involved, we believe that a number of items must be addressed before the FDA's Draft Guidance on Quality Metrics is enacted in final form. The PBOA would like to thank the FDA for this opportunity to comment. It is important to include the CDMO voice in processes like this, as industry research from PharmSource Information Services indicated that 45% of NDAs approved in 2014 utilized CDMOs.

The comments below represent a majority view of participating PBOA members who share a unique perspective as organizations providing critical services and solutions within the pharmaceutical industry. Specific or differing views may be separately presented by individual member companies in their own docket submissions.

Clarity on Roles/Responsibilities

One of the foremost areas requiring clarification from PBOA's perspective is how CDMOs' manufacturing facilities are to be defined under the guidance. The draft guidance does not explicitly address whether these facilities will be considered Covered Establishments or Reporting Establishments. We request that CDMOs be defined as Covered Establishments, while the product license holders serve as the Reporting Establishments. This would be consistent with current contractual arrangements between CDMOs and their clients (i.e., generally product license holders) and other scenarios where a CDMO assembles site operational data related to specific product reporting requirements, and relays that information to the license holder for further reporting purposes (such as Annual Report and Annual Product Review/Product Quality Review (APR/PQR) data).

Product- vs. Site-Specific Reporting

PBOA members are concerned with the ramifications of reporting on a site-specific basis, related to our request for clear definition of CDMOs as Covered Establishments. As a Covered Establishment, CDMO data reported for each product would be forwarded to the license holder for final review and submission to the FDA. We note that there are specific instances where the CDMO is responsible for subcontracting suppliers such as API vendors and other service providers such as contract laboratories. In these situations, we recommend that the CDMO collect

and review the pertinent data from those sources and forward it to the license holder for ultimate submission to the FDA. This approach aligns with contractual obligations and ensures each license holder has appropriate visibility and accountability for their products' data. This is also consistent with the practice of license holders managing regulatory authority correspondence regarding their products and providing support to CDMOs during site inspections, where product-specific discussions occur in real-time between the CDMO and FDA. Should the FDA require CDMOs to report metrics at the site level directly to the FDA, this would result in significant burden, as discussed below.

Burden

Our members are very concerned about the increased burden that would result from implementation of this draft guidance, in terms of additional resource requirements, increased IT expenditure, and reporting complexity. There is potential for misalignment on interpretation of requirements between the CDMOs and their many customers, which will require significant effort to resolve. We also believe that FDA's estimate of the time burden such a program would entail is greatly underestimated. Even with CDMOs' existing data collection procedures and capabilities, the introduction of new categories and collection requirements including CDMO vendor management, analysis and data verification will require substantial time and resource investment, which we contend has been underestimated. While we support the FDA's goals, PBOA members do not expect to receive direct benefit from less frequent inspections due to the nature of our business; CDMOs may manufacture wide ranges of product types/volumes/batch frequency in various life-cycle stages at a single manufacturing site, interface with varying tech transfer and process improvement QMS elements from multiple clients, and interact with several divisions within the FDA on various new product introductions per site. PBOA is encouraged by the opportunity for reduced post-approval change reporting, as this would be positive for CDMOs, our customers, and the patients we all serve.

Reporting Timelines

Reporting timeline cycles should be based on the anniversary dates of pre-existing APRs/PQRs in order to align with ongoing data collection, analysis activities, and contractual agreement for timing. This should also facilitate FDA review workload in aligning with the same existing review cycles and not creating additional spikes of incoming reports to review that might occur with new, uniform calendar-based timelines. Creating a new, once-a-year calendar for required reporting timelines would add undue burden for CDMOs; reporting all products for all clients in the same month would compel CDMOs to recruit and train new staff for this periodic event.

Security

In the Request for Quality Metrics draft guidance, the FDA states that it does not intend to publicly disclose quality data submissions. We would like to thank the FDA for this statement and for maintaining confidentiality. However, we would like to ensure that the documentation not be made available under the Freedom of Information Act (FOIA), due to concerns around Exemption 4 of the FOIA, namely protection of trade secrets and commercial or financial information which could harm the competitive posture or business interests of a company. PBOA is very concerned that such requests could reveal which CDMOs manufacture particular products for which clients, information that is considered highly confidential from a business and competitive perspective.

Other concerns about public availability of drug manufacturing information relate to drug supply chain security and product safety. Exposing the level of supply chain information potentially available as part of the metrics database to a global audience has the potential to have a negative impact on supply chain safety, anti-counterfeiting initiatives, and national security by opening the supply chain to those who want to damage rather than support and enhance global medicinal supply.

Additionally, FDA's maintenance of the data provided is just as important as nondisclosure of the data to the public. We request that the FDA clarify the steps it plans to take to ensure the electronic data will remain safe and secure.

Currently, the FDA is silent on its intention of sharing site ratings. ***The PBOA strongly encourages the FDA to use the site ratings only as an internal tool and to not share the rating with the site or license holder. Sharing the data either publicly or only with the sites could essentially give the same results for CDMOs — i.e. ratings will be used as a "report card" by industry to compare sites. As mentioned elsewhere in this letter, we do not believe that metrics from across variable product types, life cycle or frequency/volume of***

manufacture (such as a typical CDMO site might manufacture) will give balanced and equivalent ratings across sites. Sharing the site ratings prior to the risk scale or metrics spectrum being fully developed and understood would have negative business implications such as inappropriate competitive advantages within our industry sector that might in turn unintentionally disrupt the supply chain and impact drug availability to patients.

Legal Authority and Enforcement

The PBOA understands that the FDA is seeking to implement a mandatory program through the Request for Quality Metrics draft guidance for collection of quality data to evaluate sites for risk for drug shortage and needed inspectional frequency. We feel this mandatory program including the enforcement language will effectively result in "regulation by guidance," circumventing the rulemaking process.

Additionally, the use of "facility" in the draft guidance on page 7, Lines 250 – 256 is troubling for the PBOA. We do not want to see a scenario in which a single client/license holder fails to comply with the request for Quality Metrics, and the FDA subsequently deems ***all*** products from the CDMO's facility "adulterated." A CDMO's facility should not be considered adulterated nor issued a FDA Form 483 or Warning Letter due to a customer's reporting lapse, as this would be outside the control of the CDMO and would negatively affect other products manufactured in the site for other customers. Such an enforcement approach can lead to drug shortages and inadequate assessment of a CDMO's quality system or lead to business impact due to the label of adulteration.

PBOA's members are also concerned about the disparity between domestic and foreign facilities, with the potential for no reporting requirement on the latter. This would result in an increased burden levied on domestic manufacturers, putting them at a competitive disadvantage with foreign manufacturers. In addition, excusing non-U.S. facilities from these requirements does nothing to address potential quality issues observed at foreign manufacturing sites and could create a skewed or incomplete risk-ranking model.

To ensure the best outcome for all parties, we strongly suggest that FDA consider a voluntary, phased approach (see below) to Quality Metrics, and eliminate the enforcement portion of this guidance until the program has been operationalized and the risk/reward structure more fully understood.

Unintended Consequences/Disincentives

Depending on the data ultimately requested and the way the results are reported and/or acted upon, the program may create a set of disincentives and compliance burdens that lead to unintended consequences, such as drug shortages, barriers to entry for small businesses, and misallocation of agency inspection resources. A CDMO may have to consider whether or not to take on a difficult product/process (e.g., resulting in manufacturing deviations, test issues, reject issues, etc., which would show poorly on site metrics) since a potential negative impact on the CDMO's site rating based upon the Quality Metrics program would be a disincentive to move forward with a project, given the inherent development and reputational costs. A scenario where CDMOs must choose between taking on a difficult project or protecting a "good score" doesn't benefit the FDA, industry, or the patient. We once again urge that the metrics be kept confidential at FDA and not publicly shared.

Phased Approach

We believe the Quality Metrics initiative needs to be implemented gradually in order for all parties to gain a better understanding of the complexities, effectiveness and burdens associated with the initiative. This is similar to the approach most companies would take before rolling out such a potentially broad-impacting program internally, and may help to avoid unexpected difficulties during a more extensive rollout. We propose that the phased approach include defined evaluation periods, a metered scope of quality metrics data, representation of all sectors of the industry including CDMOs, and a reasonable grace period for inspectional observations, and ***no*** enforcement actions as the industry resolves implementation issues with the FDA. It is also recommended that a clear set of "success measures" be defined before each phase of implementation, so that effectiveness can be systematically evaluated. PBOA would also endorse that this evaluation be performed jointly by FDA, industry and a third-party consultant to ensure a broad, unbiased perspective. The use of such a third-party evaluator has proved successful for FDA in the past.

Metric Assessment

PBOA members are providing the below input for consideration for a subset of the metrics and proposed option-

al metrics contained within the Quality Metrics guidance. Additional or more comprehensive commentary on the FDA's metrics may be presented separately by individual member companies in their own docket submissions.

Product Quality Complaint Rate

We believe the FDA has recognized that complaint data should be reported by the license holder as reflected in the example data tables provided in the Quality Metrics draft guidance. Product complaint information is received and investigated by license holders. Complaints believed to be related to the services provided by the CDMO are forwarded to the CDMO for investigation. Complaints may also be reported to the CDMO that have nothing to do with the work of the CDMO, but rather to the drug product itself, the API or other reasons outside of the CDMO control. A reason for the CDMO to receive such complaints may be that the CDMO's name appears on the product labeling. If each site reports complaint data, the total number of complaints related to a product would be inaccurate.

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

It is not clear how timeliness of reporting APRs/PQRs vs. a 30-day timeline will be a meaningful measure of quality/effectiveness. The data analysis, review and report approval process impacts timeliness, and this cycle is more complex with multiple parties involved (such as when CDMOs gather and prepare data analyses). Contractually, CDMOs and clients may allow more or less time for these cycles, depending on product, process and number of parties involved. PBOA believes more meaningful quality indicators relate to the content of these reports rather than timelines of reporting.

Invalidated Out-of-Specification (OOS) Rate

Please clarify the calculation by using a formula equation with examples. The PBOA additionally asks the FDA to clarify how the results of the calculation will be used to measure quality/effectiveness and applied in a site's risk score.

The following are points to consider related to the calculation for invalidated Out-of-Specification (OOS) rate:

1) The total number of tests performed by an establishment needs clear definition. CDMOs may support both clinical and commercial manufacturing. Please confirm that only commercial products are in scope.

2) The number of batches (and therefore tests) for a particular product during a reporting period will vary. How does this impact the calculation and the metric evaluation across products and sites? What will represent statistical significance for comparison purposes?

3) Application of complex supply chains for this metric should be considered. The contractual agreement may be between the license holder and the contract laboratory, or between the CDMO and contract laboratories. Therefore, the responsibility for obtaining the information may vary on a case-by-case basis. Please provide a clear definition and requirements for the flow of data collection for all applicable Covered Establishments. For example, an API supplier providing one product to many customers may require a different approach for metric data submission than an API supplier contractually manufacturing a product for a single customer.

4) It is not uncommon for a CDMO Product Specification used for CDMO batch disposition to be only a subset of the required Product Specifications required for license holder batch disposition. We believe the FDA recognizes this by use of "or by manufacturer" in the Out-of-Specification (OOS) Result definition. As a result of this complexity, the number of tests by product may be misleading due to the overall number of tests required per the CDMO product specification. Additionally, one product may require more testing than another product based upon CDMO and license holder agreement for which site, or sites, will be performing the testing. Therefore, this fact supports our position that license holders should be Reporting Establishments and CDMOs should be clearly defined as Covered Establishments.

5) There are extenuating circumstances that may come into play for OOS stability results performed

by CDMO facilities that did not perform the packaging or assembly services for finished drug products but are managing the stability testing program. OOS failures in these cases may not reflect the quality of service provided at the CDMO but could reflect quality of service at another site, or product design issues.

6) Please clarify the scope of tests required for the calculation (e.g., analytical, microbiological, environmental, etc.).

Quality Culture

While senior management's demonstration of commitment to Quality is important for establishing and maintaining a Quality culture, the PBOA does not believe the proposed optional metrics are true measures of Quality culture. PBOA would prefer the FDA provide guidance to the pharmaceutical industry similar to medical device regulations for tangible involvement of senior management and request leveraging of established systems/regulations (e.g., 21CFR820.20, ISO 13485 standard) which requires executive management review at defined intervals with sufficient frequency. Our proposal is that the FDA use guidance to communicate this expectation to the pharmaceutical industry.

Specific Comment on FDA's Proposed Optional Metric 3

Based upon the contractual agreement between the license holder and CDMO, Continued Process Verification (CPV) performance may or may not be the responsibility of the CDMO. Even in cases where the CDMO manages CPV, license holders have the ultimate authority on regulatory change management for their product and process and therefore must approve any recommended process improvements by the CDMO, which could significantly impact the CDMO's ability to improve performance as reflected in metrics.

The Pharma & Biopharma Outsourcing Association appreciates this opportunity to submit our comments. We understand that the development of a Quality Metrics program has been a multi-year process involving many stakeholders and viewpoints, and we hope that the comments above help illuminate the specific areas of interest for CDMOs and other providers of development and manufacturing services for the pharmaceutical industry. We thank you in advance for your consideration of our requests and concerns during the finalization of the Request for Quality Metrics guidance.

Sincerely,

Gil Roth
President
Pharma & Biopharma Outsourcing Association

PBOA

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