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To: Division of Dockets Management (HFA-305)

From: Pharma & Biopharma Outsourcing Association

Subject: Comments from Pharma & Biopharma Outsourcing Association (PBOA) regarding Docket FDA-2015-D-2537: Submission of Quality Metrics Data; Revised Draft Guidance for Industry.

Date: March 27, 2017

The **Pharma & Biopharma Outsourcing Association** (PBOA) is a trade association representing Contract Manufacturing Organizations and Contract Development & Manufacturing Organizations (collectively described as CDMOs for purposes of this letter), a sector responsible for manufacturing one in every seven doses distributed to patients in the U.S. We appreciate the Food and Drug Administration's (FDA) efforts and goals to encourage continuous improvement within the pharmaceutical industry and support initiatives that possess potential benefits for patients, for industry, and for the FDA.

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. In addition, PBOA participated in the Cross-Industry Quality Metrics Collaboration Group alongside other stakeholder industry associations, and endorses the recommendations made by that Collaboration Group. We would like to express our appreciation to the FDA for granting the extension to the comment period for this draft guidance.

Executive Summary:

PBOA notes the significant nature of revisions to the previous draft guidance and appreciates FDA efforts in considering industry comments to enhance the resulting draft guidance, as well as the inclusion of a Voluntary Phase of reporting in the current draft guidance.

However, we believe the FDA continues to significantly underestimate the burden required by industry to operationalize its selected metrics, and recommend that FDA pause progression of this draft guidance and any associated data collection and engage in further conversation with industry to develop a Quality Metrics program in which the benefits truly outweigh the burden. Nonetheless, PBOA offers comments on its issues with the current version of the draft guidance.

Our paramount concern is that the role of Reporting Establishments should be limited to license holders of drugs, and not include the individual contractors/manufacturing sites that play a role in a product's supply chain. PBOA is very concerned with the apparent change of position in this guidance for CDMO establishment status, from "Covered Establishments" to "Reporting Establishments." This shift would present significant challenges and burdens to both CDMOs and license holders who work with them.

We shall address that and other concerns below.

The Quality Metrics program proposed by FDA will involve significant levels of complexity and burden for stakeholders across the pharmaceutical supply chain, and it is critical that industry has time to offer its considered perspectives.

A Quality Metrics program can only be successfully established with clear understanding of the program's goals, burdens, benefits and measures of success, as well as consistent definitions and safeguards for confidential commercial information and consensus of reporting requirements. This current draft adds clarity, specific examples, and some explanation of the benefits that would accrue to FDA and drug buyers, but additional clarity is needed, and the current draft has raised significant new topics that must be addressed if FDA intends to move forward.

Regarding the goals and benefits of the Quality Metrics program, PBOA asks for clarification and specific outcomes of how the metric information will correlate to reduced inspections. How will the data be factored in to overall inspectional risk? How may post-approval change burden be reduced? How may drug shortages be reduced through the implementation of the specific metric elements for site and product reporting? We note that the benefits to industry are not clearly defined nor are criteria established for how those benefits will be realized. We further believe that some potential benefits, such as reduction of post-approval change burden and inspectional relief, will not be equally realized by all participants in a product supply chain, such as CDMOs, due to the nature of their roles (i.e. serving multiple clients for varied products; not direct product license holders).

In addition, it is unclear as to whether the major goals of the Quality Metrics program are reconcilable. The product-related metrics necessary to predict and alleviate drug shortage situations might be at odds with the site-related ones that could assess quality at a facility level. Metric data can lead to inaccurate conclusions. A product-related metric, like Lot Acceptance Rate (LAR), for example, may imply a quality issue with a product process where the true root cause may be facility or equipment related. It is unclear how the metrics identified in this Guideline will lead to insights that will help predict, and possibly mitigate, drug shortages.

As stated earlier, PBOA believes that FDA significantly underestimates the burden of collecting these metrics across the complex supply chains of many products produced today. A given product's supply chain commonly involves multiple facilities/entities within a single company, CDMOs, API manufacturers, repackagers, contract laboratories, and other segments of the industry, resulting in complex business relationships that require extensive management; this must be taken into account for this program and its practicality in any implementation of a Quality Metrics program.

Integration of mandated, defined metrics into this business matrix will take immense effort and time, and the required reporting framework -- including procedural alignments, revised contractual agreements between CDMOs and license holders, and details of approval of CDMO metrics for release to FDA by license holders -- will generate additional challenges to manage. These must be worked through on an individual basis before any reporting can be initiated, and may affect a company's ability or willingness to report during a voluntary phase. These challenges should also be taken into consideration when planning the timelines for initiation of the program and the required reporting periods.

If the FDA chooses to proceed with this initiative, we believe that additional modifications and clarifications to the draft guidance are needed before a Voluntary Phase is initiated, as well as after the evaluation of the results of the Voluntary Phase. FDA should engage in a scaled-down trial period during which participants submit metrics on a single product to test the system.

The sections below address some areas more specifically.

Product and Site Reporting:

PBOA strongly asserts that Reporting Establishments -- i.e., those that actually submit the metric data to FDA -- should be limited to license holders, and not include the individual contractors/manufacturing sites that play a role in a product's supply chain. We further contend that reporting should be done by product rather than by manufacturing establishments. The reporting establishment requirements should not apply to CDMOs or to API

manufacturers when they are not license holders of products, as they only possess a limited subset of data relating to a license holder's product, depending on the contracted scope of work, with little or no visibility of other data important to the metric collection for a given product. Only the license holder would be able to integrate those metrics for FDA's purposes.

Furthermore, CDMOs generally perform contract work at a single site for multiple products (and sometimes different types of product operations, such as finished drug manufacture, drug substance, bulk packaging, secondary packaging and labelling), employing multiple technologies, and for a variety of clients (with different product profiles), which makes any meaningful comparison across the variable range of services and products manufactured or tested at a given site of very limited value as a quality indicator for the proposed metrics (or for any standard set of prescribed metrics). For example:

- Comparing **LAR** across different product types and operations; how lots are constituted, how many units per lot (large campaigns or small batches). The numerator in this case could vary widely and make for poor comparisons across multiple products of varying attributes and complexity.
- **Product Quality Complaints** – a CDMO likely only sees a very limited portion of the full range of a product's complaints from the license holder, and different products may have very different complaint profiles, so there is no way to relate that meaningfully to a site-level metric for a CDMO.
- For **Invalidated Out-of-Specifcation** (IOOS), the requested metrics will be of limited use in looking at multi-product/multi-client sites, as products and their associated methods are of different complexities and the methods are often owned by the license holder, which may include varying designs and robustness. Additionally, the intended use of the test by the license holder (e.g. used to support investigation, development, clinical product, commercial products, etc.) is often not known by the contract test laboratories. Comparisons of IOOS across products and for various license holders may result in poor correlation to site testing capabilities.

PBOA believes that CDMOs would not see a benefit of reduced regulatory requirements, such as inspectional frequency or post-approval change management, for the reasons stated above. PBOA proposes that CDMOs should only be responsible for reporting product metrics to individual products' license-holder clients. The Reporting Establishment (i.e., license holder) would specify the technical reporting requirements with the individual CDMO or API manufacturer in the applicable Quality Agreement. We propose that, if CDMOs must submit to FDA, the submission would consist of a list of products and report types that will be provided to license holders, thus registering that requisite reporting is ongoing. This aligns with the position that the license holder is responsible for CDMO activities and data, and should therefore be the entity reporting data to FDA.

Supply Chain Complexity:

Attachment 1 provides an illustration of the supply chain complexity and multiple metrics-generating points for a single drug produced by CDMOs for a license holder.

Burden:

It is important to note that, while a stated goal of this program is to reduce overall burden on FDA and industry, the metrics approach proposed in this draft guidance would significantly increase the burden on industry, specifically in the CDMO sector, which accounts for approximately one in seven (1 in 7) doses distributed to patients. For all of industry, the number of elements to be reported under the LAR, Quality Complaints and IOOS metrics has been clarified and currently results in more data points being reported than was indicated in the previous draft. Additionally, the proposed reporting by both product Reporting Establishments and site Reporting Establishments would mean that CDMOs (per site) would have to report metrics to multiple individual product license holders and also across all products manufactured at a site directly to FDA. This effectively doubles the reporting that all CDMO sites would be required to perform, likely with very different formatting and parsing of data for the two reports. This could also lead to confusing and potentially inaccurate data.

Additionally, requiring quarterly reporting of these metrics as opposed to an annual basis would increase that burden on CDMOs. PBOA suggests that the reporting frequencies be annual, to align with PPR/APR/PQR anniversary dates, both for burden reduction and to align with other analysis frameworks that exist for the different metrics already being reported to license holders.

For contract laboratory sites, the IOOS metric reporting will constitute an extreme burden. APRs are generally not published for laboratory test-only clients. Reporting of this metric would be an entirely new process in these cases. Further, as stated above, it is not always clear from clients whether the scope of contract testing is for commercial, clinical, investigational or other activities, making it impossible for the CDMO to parse these activities for reporting to accurately reflect on site quality per the draft guidance.

Quality Agreements between various sites and parties (e.g., license holder and CDMO) are paramount to clearly defining roles and responsibilities of each party, and in turn critical to maintaining uninterrupted supply of quality drug products to the market. These Quality Agreements and related contracts contain confidentiality requirements, such that each of a CDMO's clients would also require review and approval of site establishment metrics related to their products before a CDMO could report to FDA. This will create an immense amount for work for CDMOs over and above metrics already captured in our Quality Management Systems and monitored by our license-holder clients, and will incur the need for substantial additional resources and accompanying costs. We believe this potential burden and associated costs are significantly underestimated by FDA.

FDA must also understand that each and every Quality Agreement will need to be modified to accommodate the FDA reporting requirement and the exact metrics specified (potentially in a compressed timeframe along with all of industry who employ CDMOs and other contractors), which will create a substantial revision and review burden for CDMOs' and clients' Compliance and Legal teams. This will involve time and cost, and must be considered when calculating burden and comparing to benefits, as well as overall implementation timelines. It is not feasible for an entire industry to revise every one of its Quality Agreements in the span of a few weeks.

FDA states that it expects most of the Quality Metrics data described in the revised draft guidance are already collected by establishments as part of Periodic Product Review (PPR). This is not the case. FDA has defined its metrics very specifically to suit its purpose. Companies do use metrics as part of PPR, but these metrics are defined to suit the companies' purposes, unit operations, and specific needs, not necessarily as FDA has defined them.

Retooling these metrics for FDA's purposes will strain industry's finite resources and potentially shift attention away from continual quality improvement initiatives.

Metrics:

As mentioned above, FDA is mistaken in its understanding that most of the Quality Metrics in this draft guidance are already being collected by establishments as part of conducting PPR, as companies and sites use metrics specific to their products, processes and systems. The proposed metrics will be additive to those already collected. Specific comments and questions on metrics are listed below:

Product Quality Complaint Rate (PCQR)

- The product license holder is responsible for oversight of product quality complaints, and they disseminate information to various supply chain CDMOs/ participants. PBOA asserts this should be a product reporter-only metric. Contract sites will likely only see a subset of the total complaints for a product, so their reporting would not be meaningful for the product view, and should not be compared across various product types and operations on a given site, as these profiles will differ greatly. Also, the timing of the complaints versus timing of production will not align, and would further dilute the value of the metric (e.g. campaign manufacture vs. multiple batches per monitoring period). In addition, CDMOs will not always know in which markets a product is distributed specifically, and thus may or may not know whether a specific complaint should be reported to FDA. This would be a product reporter's responsibility.

Invalidated OOS Rate (IOOSR)

- Allowing two options for date that an OOS result is counted may produce misalignment between CDMOs and license holders. Use of a single specified date (e.g., the day that an OOS investigation is initiated) is preferred.
- The invalidated OOS Rate may not be the appropriate term as the metric appears to be combining confirmed OOS and invalidated OOS data.
- Definition of which tests are supporting the labeled expiration date (e.g. stability tests only vs. additional tests for characterization), per line 308 from the draft will now be required to be understood between the CDMO/ contract laboratory and license holder, as this information is typically only understood by the license holder.

Lot Acceptance Rate (LAR) Data

- The defect example starting at line 742 does not align with real-world contractual scenarios; when there is disagreement about rejection. A CDMO should not have to change its metric based on a disputed rejection from another party.
- When a CDMO performs subset operations (such as bulk vs. finished packaging) would this need to be included as a secondary operation?
- We request clarification on timing of initiation of reporting and when post-approval clinical manufacturing using the same process and controls as a commercial process do or do not need to be reported. Should reporting begin following FDA commercial approval and include batches from the performance of process performance qualification (PPQ)? Should clinical batch manufacture for material intended for clinical trials OUS be excluded even though process is the same as the commercial process? It is important to note that this knowledge would typically be license holder-specific and not shared with the CDMO, thus not reportable by the CDMO.

Data Security and Confidentiality:

Under client/CDMO or API manufacturer Quality Agreements, license holders and CDMOs consider metrics data to be Confidential Commercial Information per 21 CFR 20.61(b) and both parties would expect FDA to follow existing protections for this category of information as well as implement reasonable protections against electronic theft or unauthorized access. We feel strongly that data security is paramount to the success of any Quality Metrics program that includes site-specific information. Data security should be prominently addressed in FDA's guidance document, along with assurances for how data security will be maintained.

We are also concerned with how this information may be shared with other international regulatory agencies, per inter-agency cooperative agreements and sharing practices, and what privacy and security the data will have in any such case, as well as how it may be used by other agencies. We request clarification on this.

We request that such confidential data should not be subject to Freedom of Information (FOI) requests, not only during the proposed Voluntary Phase, but also upon adoption of any Final Rule and/or Final Guidance.

Public Reporting:

Under the currently proposed rating system -- i.e. related to how a site reports quality data, not the content of the data they report -- CDMOs could confidentially report to FDA the list of products manufactured and tested at a CDMO site and the clients to which data related to those products has been reported, per guidance metrics. This is a potential alternative to site-based reporting and the proposed rating system, which is dependent on clients meeting their reporting obligations under the guidance and contractual agreements between the client and CDMO. This would preclude a CDMO being penalized due to untimely or incomplete reporting by the license holder.

We strongly object to public posting of a list of reporting sites. Patients, consumers, healthcare purchasers and providers may associate the willingness to report and the resulting FDA rating with the quality of products produced by the reporter, and may consider omission to be a sign of poor quality. There is no statement as to how the reporters' list reflects on product quality or site performance, which are inherently more impactful indicators for patients, purchasers and providers when making their sourcing choices. PBOA would like clarification on how the rating system will align with intended purposes of reporting Quality Metrics.

We also request an appeals process in the event that there is disagreement over a rating assigned under the proposed system.

Program Evaluation:

We believe that, once the current comments are reviewed and revisions made, and after any revised Voluntary Phase, there should be an additional comment period and public meeting to review overall program results (specific outcomes), successes, issues raised and to discuss next steps. We strongly recommend use of a third party to independently evaluate the success and benefits vs. burden of the program, as well as periodic stakeholder meetings similar to User Fee Act implementation meetings.

The program as outlined in this draft may provide little incentive for CDMOs and other contractors to par-

ticipate in the Voluntary Phase until more is understood about how the data is to be used by FDA, how it will be shared publicly and across other agencies, how confidentiality and security will be treated, and how reporting will be linked to quality indicators. At present, we do not see how a CDMO will get any regulatory relief based upon the sheer range and number of products and clients to which we provide contract services, and since we are not product license holders as defined in this letter. If FDA chooses to proceed with a Quality Metrics program, we request a trial period during which product-reporting participants submit metrics on one product to test the system and learn, to truly phase this program in. This may help incentivize participation.

As an active participant in the Cross-Industry Quality Metrics Collaboration Group (a broad informal group of trade and technical organizations across the pharmaceutical industry), we support that Collaboration Group's approach on the Quality Metrics Draft Guidance. We agree that further progress toward data collection under this draft guidance should be paused and that FDA must engage with industry to develop a full assessment of the burdens and benefits of Quality Metrics before any revised program is proposed.

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.

Sincerely,

Gil Roth
President
Pharma & Biopharma Outsourcing Association

PBOA

MEMBER COMPANIES

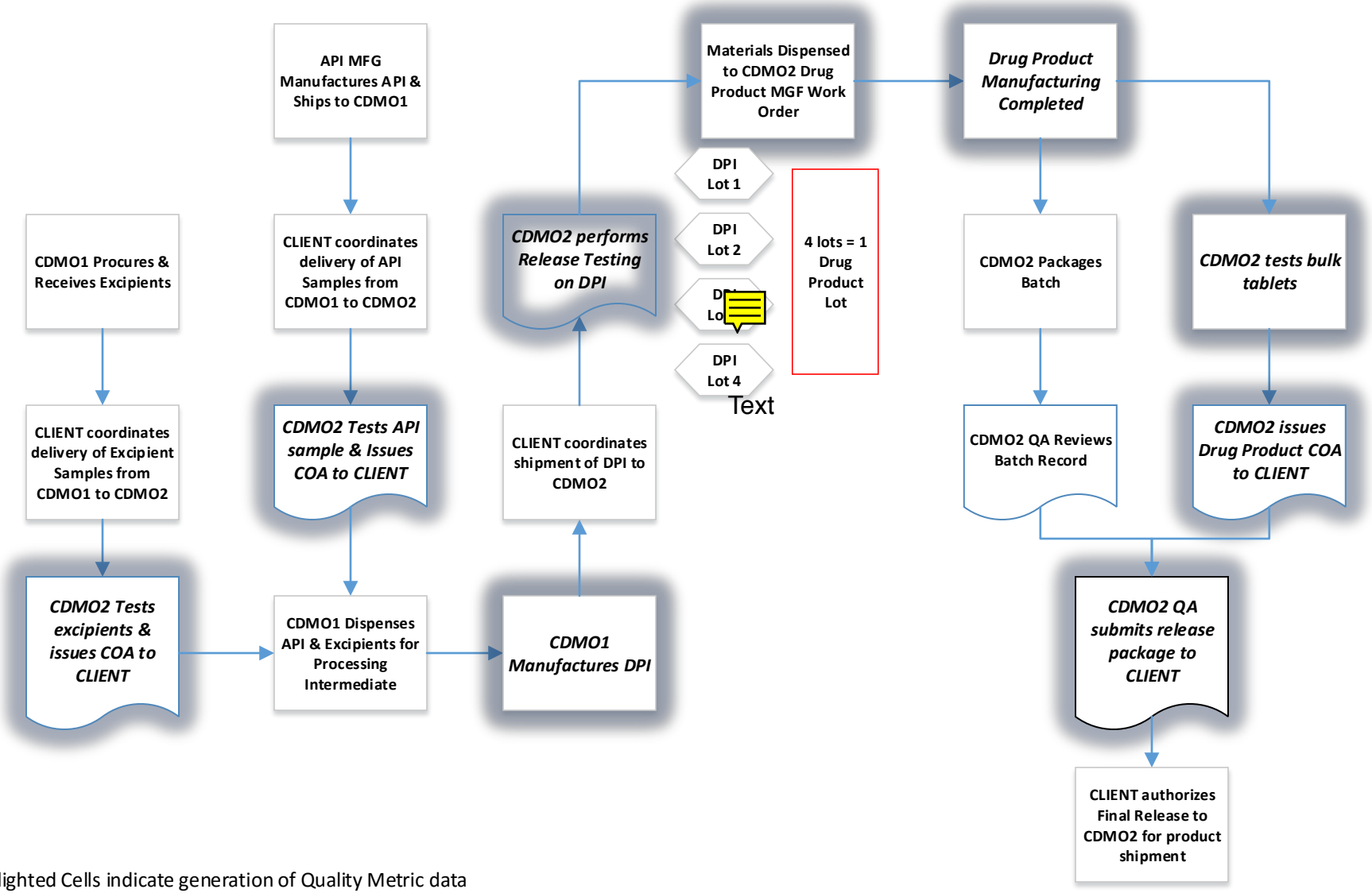
3M Drug Delivery Systems
Afton Scientific
Alcami
Althea CMO
AMRI - Albany Molecular Research, Inc.
Baxter BioPharma Solutions
Catalent Pharma Solutions Cook Pharmica
CMIC CMO USA
Coating Place, Inc.
CPC - Contract Pharmacal Corp.
DPT/Confab
Ei, a Pharmaceutical Solutionworks
Emergent Biosolutions
Groupe PARIMA
Halo Pharma
IDT Biologika
Jubilant HollisterStier
Lyophilization Services of New England (LSNE)
Metrics Contract Services
Mission Pharmacal/ProSolus Pharma
Patheon Inc.
PCI Pharma Services
Pfizer CentreOne
Pharma Packaging Solutions
Piramal Pharma Solutions
Tapemark Inc.
Therapure Biomanufacturing
WellSpring Pharma Services

AFFILIATE MEMBERS

Houlihan Lokey
INTERPHEX
Millrock Technology
PharmSource
SafeBridge Consultants
SCORR Marketing
TraceLink
Vantage Consulting

ATTACHMENT 1:

Multi-CDMO Drug Product Process Product Flow



Highlighted Cells indicate generation of Quality Metric data

Two Client/CDMO2 Quality Agreements at CDMO2; one for Analytical API through DPI Release, and one for Drug Product Manufacturing and release