PDA Global Headquarters
Bethesda Towers,
Suite 600
4350 East West Highway
Bethesda, MD 20814 USA
TEL: +1 (301) 656-5900
FAX: +1 (301) 986-0296

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

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

Reference: Docket No. FDA-2022-N-0075 for "FDA Quality Metrics Reporting Program; Establishment of a Public Docket; Request for Comments."

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to FDA as the agency further refines the Metrics Program. PDA continues to support the FDA's focus on the pharmaceutical/biopharmaceutical industry's use of quality metrics as an important component of continual improvement. PDA believes that the use of metrics as a tool in understanding performance is an important part of improving processes, systems, and culture. To be effective and successful PDA believes that the FDA Metrics Program should avoid becoming a strict compliance requirement (for example inspectors arriving at a site with a metrics report in hand) as that would likely lead to unintended consequences and behaviors that are counterproductive to developing a good quality culture and continuous improvement mindset. This may occur especially at sites with less mature quality systems that might over-emphasize having "good" metrics results rather than focusing on learning from the metrics to further continuous improvement of the underlying systems and processes. Periods of time where there is an increase in variability of specific metrics will occur for even the best performing site for reasons that must be considered when evaluating the data.

PDA feels that promoting a site's use of quality metrics as part of their Quality Management Maturity (QMM) assessment process would drive improvements in the manufacturing site's state of quality culture and produce the best outcomes for the site, the products they produce, and ultimately the patients they serve.

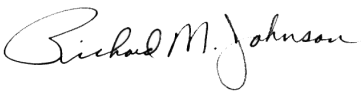
The novel approach for the Metrics Program, proposed by the FDA via a Federal Register notice on March 9, 2022, of allowing a site to select the metrics from within a specified practice area that is most appropriate to their operations and best characterize the maturity of their site or the opportunity for improvement is a positive development for the industry. PDA has long championed the idea of using trends in metrics over time to evaluate the performance of a site against its own history rather than comparing point-in-time results to other sites. This new FDA

proposal appears to be consistent with this approach. We present our comments in the attached document.

PDA is a non-profit international professional association of more than 10,000 individual members scientists having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,



Richard Johnson
President and CEO

cc. Glenn Wright, PDA; Carrie Horton, PDA

Reference: Docket No. FDA-2022-N-0075 for "FDA Quality Metrics Reporting Program; Establishment of a Public Docket; Request for Comments."

General Comments

To allow a better understanding of the metric data provided, PDA recommends that FDA include a field within the Metrics Program reporting which allows a site to provide context alongside the metrics data particularly when there has been a change at the site such as an introduction of a new product, implementation of a process change, automation of a quality system, or installation of new equipment. These examples could lead to increased variability in site metrics data. It would be useful to proactively flag such situations for FDA in a text field that accompanies the data.

While the draft provides a better understanding of the FDA's current view, the industry still has several questions where additional detail would be helpful, such as:

- How will the metrics data be used internally at FDA?
- What type of connection is foreseen between the Metrics Program, the QMM Rating System, the Risk-Based Inspection Model, and the Remote Assessment Program?
- What type of communication should a site expect from FDA after the submission of metrics data?

  For example:

  - Will FDA contact a site with any signals they have observed in the data and offer to proactively assist with a potential drug shortage or will observations about a site's metrics data only be shared by investigators during an inspection?
  - Will a site have the opportunity to provide context around potential signals seen in the metrics data either at the time of submission of metrics data or later when a potential signal is detected by the FDA?

- Are there plans to clarify that the metrics program is intended for commercial-stage products (i.e., approved Biological License applications (BLA), New Drug Applications (NDA), or Abbreviated New Drug Applications (ANDA)) and not clinical-stage products?
- Will FDA want Marketing Authorization Holder (MAH) to submit product-specific metrics and manufacturing sites to submit site-specific metrics?
- Will the FDA be clarifying the mechanism for reporting in the Metrics Program? Does FDA envision that there will be a separate reporting mechanism established for all metric reporting or will FDA propose to use an existing reporting mechanism, e.g. Annual Reports?
- Will FDA be compiling the data for all products from a CMO site and then analyzing the metrics across products for that CMO?

PDA responses to the questions for the Public Docket

A. Reporting Levels

1. **Do you agree that reporting should be aggregated at an establishment level?**
   a. Looking at metrics by site and reviewing trends over time is a common approach within pharmaceutical manufacturing business practice. However, the context of the metrics

needs to be taken into consideration given the nature of the site and variation in the product mix manufactured and there are some metrics (e.g., CpK and PpK), that make more sense to report from a product level due to the goal of the metric. PDA recommends that FDA also provide sites with the option to report at the product level aggregated by site based on the metric they choose to report.

2. **Would reporting at an establishment level facilitate submission of quality metric data by contract manufacturing organizations?**
    a. Different clients have different tolerance about what a CMO can report to the FDA, so the CMO PQS has to be flexible, and the quality agreements will control what data can be disclosed. Often a CMO will look at metrics by product and client, to facilitate process improvements. Types of processes may be significantly different across different clients at the same site, especially for a large CMO. Variability in the frequency of production of certain products will also contribute to the variability of metric updates. FDA should provide flexibility for CMOs in their metrics reporting by site or by product. PDA recommends that a CMO report data that demonstrate PQS effectiveness and are consistent across all clients, such as general facility, utility, and other site metrics, directly to the FDA.

3. **If you normally assess metrics by product family at an establishment, what are useful definitions of "product family" from your industry sector?**
    a. PDA recommends defining a "product family" by manufacturing and analytical testing methods that share a common platform technology, such as aseptic processing/filling, or tableting, in order to compare variability against relative technology capabilities. PDA recognizes that this may be a challenge for CMOs that produce metrics against specific clients and products and recommends that the FDA provides flexibility for CMOs in their metrics reporting.

B. Practice Area and Quality Metrics

1. **If you think the general practice areas listed in section II of this notice would not meet the objectives of FDA QM Reporting Program, what other practice areas should FDA consider?**
    a. PDA recommends FDA consider rolling out the metrics collection by letting a site select one practice area for its initial metrics reporting. This will give industry and FDA time to work through the challenges of collecting and submitting metrics through this new program with a smaller set of data and then the program can build forward adding additional practice areas over time. PDA recommends starting with the manufacturing process performance for manufacturing sites or the laboratory performance for laboratory sites. If a site conducts both types of operations the site should be able to select one practice area for initial metrics reporting. PDA does have concerns with proposed metrics reporting for the practice areas of supply chain robustness and quality system effectiveness and recommends additional discussion be had to understand the implications, value, and resources required to submit metrics on these two additional areas.
    - Although PDA appreciates the close connection between the FDA Metrics Program and the goal of preventing and mitigating drug shortages, the practice area of Supply Chain

Robustness within the FDA Metrics Program seems to be an additional burden on top of the data FDA is requesting under the new CARES Act 510(j)3 reporting. It would cause unnecessary work and potential confusion for the industry to be asked for Supply Chain data in two different formats, across different timeframes and reporting processes. PDA requests FDA to clarify why data from both programs would be needed.

- PDA recognizes there is a need to establish a process for evaluation of a site's PQS effectiveness as part of the implementation of ICH Q12. Additional measures to provide evidence of quality system effectiveness, such as annual product/process reviews, quality system reviews, data on complaints and recalls, etc. should also be considered in the determination of PQS effectiveness. PDA believes that the level of regulatory oversight of post-approval changes should be proportional to the effectiveness of the PQS. PDA strongly supports the idea that sites and companies with a strong PQS should be recognized and be given regulatory discretion or flexibility such as reduced reporting categories for post-approval changes or reduced frequency of site inspections. FDA's selection of Quality Systems as one of the four practice areas supports this goal.
- There is concern within the industry about how the collection of, and reporting to, FDA of individual metrics for PQS effectiveness could create unintended consequences in site behaviors, such as resistance to adopting new technologies or even stifle continuous improvement for fear of impacting the reported metrics. PDA recommends quality system effectiveness is better assessed through site inspections and with a maturity model approach but would like to see swift implementation of the QMM Rating system or similar to ensure the implementation of regulatory flexibility associated with Q12 for those companies that have effective quality systems.

2. **If FDA were to consider Quality Culture as one of the general practice areas, what are the critical components of a robust quality culture and can any of these components be measured quantitatively? If so, how do you recommend quality culture information be captured as a quantitative metrics (e.g., near misses, APR on-time, binary response to Quality Culture survey, or other numerical metrics. KPI's)?**
    a. PDA believes Quality Culture is not easily measured through quantitative metrics but is better evaluated by interviewing staff and assessing quality system elements and behaviors against a maturity model. By understanding the presence and level of utilization of various systems, such as QRM and knowledge management, that drive favorable behaviors, the maturity level of a quality culture can be measured, thereby creating the opportunity to track progress towards greater maturity.
    b. PDA further recommends any reporting of Quality Culture metrics to FDA should be established based on a transparent discussion of the learnings and outcomes of the FDA QMM pilot programs and further clarity on how the QMM Rating system will be established. PDA also recommends that CDER consult with CDRH on the learnings from their Capability Maturity Model Integration (CMMI) Case for Quality pilot program which began with an overall culture assessment and was followed by metrics gathering.
3. **Do you think that any of the examples of quality metrics proposed by FDA would not be appropriate measures for the designated practice areas?**
    a. PDA believes that an overly specific focus on any metric result, especially in the case of timeliness metrics, rather than the underlying goal of continuous improvement can

inadvertently create a "compliance mindset" leading to behaviors and conditions that undermine a speak-up culture. PDA is developing a publication to help educate the industry on the pitfalls of mis-using metrics and provide guidance on how to use metrics in the appropriate context. Some examples of metrics that may become problematic:

- CALIBRATION TIMELINESS: A calibration metric focused only on the timeframe/conformance to schedule may lead to unintended behaviors to meet compliance expectations. PDA recommends looking at how or why assets may have drifted out of calibration instead such as: tracking assets out of tolerance (OOT) found during the period between calibrations. Another example is the number of work orders related to recalibration initiated in response to a corrective action.
- REPEAT DEVIATIONS: Repeat deviations is an important metric for a site to use in understanding CAPA effectiveness and site remediations. Converting this to an FDA reported metric may drive the wrong/improper behaviors such as "not speaking up on quality/compliance" leading to potential for underreporting of non-conformances/deviations, or changes in the definition of "repeat deviation" to reduce the frequency of occurrence and improve the appearance of this metric.

4. **What other metrics should FDA consider for a designated practice area?**
    a. FDA should focus on metrics that clearly drive a thorough understanding of a product's manufacturing and testing processes for CQAs to reduce true variability. We believe allowing firms and sites the flexibility of defining their own Process Capability Indices, Method Performance, and associated action levels, would drive a continuous improvement mindset and reduce product variability and help ensure product supply.
    b. As an alternative to IOOS, measuring method performance either by overall invalids or by measuring the variability around control or standard can be a better measurement of the robustness of a method and the lab performing that method.
    c. Time to product disposition is a measure of the consistency of a specific process and is a valuable predictive metric for individual products. This timeliness metric is best placed to be controlled internally under appropriate QMS requirements as distinct from an FDA metric. As with all timeliness metrics, there is a risk of incentivizing behaviors that focus on a good result rather than the underlying root cause so this may be a better internal site metric than a metric reported to FDA. In addition, disposition timelines can vary dependent within a site/organization and can change over time due to stage of the product lifecycle (CT/PV/commercial), processes subject to change management.
5. **FDA is interested in an establishment's experience with implementing process capability and performance metrics. For example, how would you report Cpk and/or Ppk to FDA as part of the QM Reporting Program (e.g., reporting Cpk and/or PpK for certain products, aggregated at the establishment level)?**
    a. PDA proposes allowing a site to define their statistical methodology for measuring Process Capability (PpK, Cpk, etc.) against a product's CQAs would help drive firms to continuously improve the product variability. Similarly, allowing sites to define their Method Performance by an analytical platform helps to identify variability and drive continuous improvement of analytical methods. PDA believes it is more appropriate to report process capability at a product level rather than a site level so that the variability

of individual processes is not hidden. This is especially true for CMO sites that are managing several different processes, products, and marketing authorization holders.

b. Another caution with Capability Indices is that newer companies or new products with only a very few lots made may not have enough data to calculate process capability. This can be especially problematic for very small volume products, such as less than 5 lots made per year. FDA should be open to discussing older product specifications and CQAs to be sure capability metrics are being set on clinically relevant specifications and CQAs. It's important to understand variability from both the process and method contributions.

c. PDA would also like to highlight a proposal for a process risk index (Rpk) as described in Gunter, Coleman et. al.[i] This concept is very new and not yet endorsed by PDA members. However, this paper claims that instead of relying on traditional data summaries such as means and standard deviations to characterize process results, the proposed index uses sample quantiles and a visualization approach. Quantiles are more accurate and reliable when data are skewed or short-tailed as is often observed for pharmaceutical processes. These authors propose that Rpk is more informative if a process is not stable or not in statistical process control.

6. **A metric may need to be changed or adjusted by an establishment to better monitor PQS effectiveness, inform appropriate business strategy, or capture insightful trends, thereby driving continual improvement behaviors. What criteria should be applied to justify changing or modifying a quality metric (by either establishment or by FDA)? How frequently would you expect changes or modifications to be needed?**

   a. PDA agrees with the observations from the Harrison and Schniepp 2015 Pharm Tech article "Metrics of Quality Culture" that "site management needs to be cognizant of the fact that whatever metrics are reported they must be developed, evolved and adjusted over time to maximize their impact on driving positive change. Each site should use careful thought and consideration when determining what to measure, how often to measure, how to interpret and communicate the data, and what the expectation is for using the data to drive positive change."[ii] In order to enable this, a site should also have the ability to change a definition of a metric or selection of a new metrics based on learning by the site and with justification to FDA. Changes in metrics should be accommodated when a firm makes a process change or platform technology change or adds a new product. A site could use the Annual Report to notify FDA of any changes in reported metrics and provide explanation such as new definition, new metric selected for a practice area or expected change in values due to a process or equipment change. However, a metric change should never be considered a regulatory commitment, established condition nor require a regulatory change notice to the filing.

   b. PDA strongly recommends the metrics program reporting include a free text field or other mechanism for the site to explain to FDA the context behind any change in definition or results of metrics.

7. **When would you rely on multiple metrics versus a single metric as an indicator when assessing a particular proactive area (e.g., two metrics are considered in combination because one metric influences the other)? What combination of metrics have been meaningful and useful?**

a. One good example of metrics that are interdependent is process and method variability. To understand true process variability, one needs to also understand analytical method variability and noise. These two metrics complement each other to drive continuous improvement in both the process and methods utilized. Tracking process capability all by itself does not tell the whole story because the contribution of method capability must also be factored into any root cause investigation of variability.
b. Repeat Deviations are a good complementary metric to confirm whether the CAPA Effectiveness metric is appropriately defined. As noted above: Converting this to an FDA reported metric may drive the wrong/improper behaviors such as "not speaking up on quality/compliance" leading to potential for underreporting of non-conformances/deviations, or changes in the definition of "repeat deviation" to reduce the frequency of occurrence and improve the appearance of this metric.

C. Other Considerations

1. **Are there considerations unique to specific product categories (e.g., generic drug products, OTC drug products, or biological products) that should be addressed in the QM Reporting Program?**
    a. Yes, PDA recognizes that metrics such as process and method capability would be influenced by the technology platforms and dosage forms the product utilizes rather than the category it falls into. Additionally, metrics may be more representative of site maturity when considering product types that are more well-characterized with newer process controls and validation paradigms. Similarly, metrics from sites with very high-volume products (e.g., generics or OTCs) are likely to show more meaningful trends because of the number of data points. FDA should give consideration to metrics from sites that make only a few lots per year or a large variety of disparate product types or products that have variable seasonal demand.

2. **What would be the optimal reporting frequency for quality metrics data submissions (e.g., monthly, quarterly, or yearly, and segmented by quarter or monthly)?**
    a. PDA recommends that annual reporting of metrics broken down by month is the least burdensome approach. PDA also suggests that FDA consider starting metrics reporting with a phased-in approach to reduce burden on industry. Another suggestion is to consider reduced reporting frequency for older, well -established products or sites that have demonstrated high levels of quality systems maturity.

3. **In instances where a manufacturer is not able to extract domestic data and its submission to FDA contains both US and foreign data, how can these data be submitted to FDA in a manner that would still be informative?**
    a. PDA recommends that companies have the option to include data on all products manufactured to FDA specifications, whether distributed to the US or OUS when compiling a metrics report to the FDA.

4. **Are there any other aspects of FDA's proposed direction for the program that FDA should address in future policy documents?**

a. PDA believes the ideal state of the FDA metrics programs would be for FDA to collect high-level metrics from organizations that are better suited to drive the right behavior of continuous improvement in both manufacturing and analytical laboratory operations. This is possible with sufficiently mature quality organizations and would allow firms and sites to monitor other metrics internally for various systems (e.g., CAPA Effectiveness, Right First Time, Calibration Timeliness, etc.) in a similar way that firms use internal audit assessments as a means of an internal health check to prepare for health authority inspections.
b. While FDA has to design a program that works also for organizations that do not have mature systems, the collection of lower-level metrics does create the risk of continuing to drive a compliance mentality at sites which can undermine a mature quality culture and the ability to understand true root causes of quality problems.
c. It would be useful for FDA to discuss in future metrics program communications the possible unintended consequences of focusing solely on the monitoring of timeliness metrics without a positive quality culture and leadership culture.
d. In future Metrics Program publications, industry would also like to see more transparency on how these quality metrics will be evaluated by the FDA and the intent of how the agency will respond to identify and mitigate quality risks, and if the agency will be actively or passively involved in the follow-up actions. A case study example would better inform industry on how the data will be reviewed and analyzed, and what FDA actions might occur as a result.

[i] Gunter, Coleman, et. al, "A Risk Index and Data Display for Process Performance in the Pharmaceutical Industry" PDA Journal of Pharmaceutical Science and Technology March 2018, 72(2) 1880198;
[ii] A. Harrison and S. Schniepp, "The Metrics of Quality Culture," Pharmaceutical technology 39(9) 2015.