PDA
Parenteral Drug Association

Connecting People, Science and Regulation ®

Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

November 23rd, 2015

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Guidance for Industry Request for Quality Metrics
Docket: [FDA-2015-D-2537]

Dear Sir/Madam:

PDA appreciates the involvement FDA has had with industry stakeholders on the development of the Quality Metrics program over the last three years. PDA agrees with FDA that the key drivers of the quality metrics program are to enhance pharmaceutical product quality and prevent drug shortages for patients by allowing FDA to focus compliance resources on high risk establishments and to reduce regulatory burden of onsite inspections and prior approval changes for those sites deemed low risk based on FDA's risk-based inspection model. PDA's detailed comments on the draft guidance are enclosed.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by our Pharmaceutical Quality Metrics Task Force (a committee of experts with experience in pharmaceutical manufacturing and quality) and reviewed and approved by our Regulatory Affairs and Quality Advisory Board, and our Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President & CEO, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

Food and Drug Administration Draft Guidance
Request for Quality Metrics
Submitted Nov. 23, 2015

General Comments	Rationale
1. Based on Industry's experience implementing metric programs, PDA suggests that the evaluation period should be two years after the formal collection of metric data is initiated. This evaluation would formalize the metric journey into key milestone events and assessments prior to implementing the final data in FDA's inspection risk-based model for official scheduling of site inspections. This evaluation period could entail a number of assessments against expected outcomes with results reported back to industry, and could include: a. Applicability: Metric and definitions are applicable across the industry – During the assessment period, allow firms to submit comments on why the current metric assessment and / or metric definition are not applicable for their product. Assessments should include a reporting percentage of missing metric data due to nonalignment of product type with metric definition. Is there a need to modify or clarify metrics or definitions to encompass entire industry product populations based on submitted comments during the assessment period? b. Differentiation: Ability of the data to differentiate sites / products– Does the metric data allow the sites to be categorized as quality higher risk sites or lower risk sites? Assessment: Use statistical tests to show relevance of data by generating a population curve from high quality to lower quality sites. FDA to identify the number of sites that would have seen a reduced inspection burden if the data had been used in the inspection risk-based model.	This proposal will facilitate a faster implementation and help assure the success of the program by assessing five areas and making the appropriate modifications to evolve the program, or determine the value is not worth the extra burden to industry and FDA.

General Comments	Rationale
c. Reporting assessment: Is the reporting optimized to minimize industry's ongoing burden (man-hours) for submission and FDA's use of the data? Allow firms to submit suggestions on optimizing collection of data. Assessment: Assess optimization suggestions and rerun the burden assessment with an independent firm to provide an updated value and more realistic value. FDA to outline the working assumptions on additional burden activity beyond existing GMP data collection. What would be the proposed benefit for FDA, patients, and Industry to offset this increase resource burden? This might include estimated resource saving from fewer inspections, faster post-approval changes, identification of potential drug shortages, and a possible shift in the two- year assessment period on improved metrics of higher risk sites / products. d. Assessment of Unintended Consequences: gather evidence (i.e., 483 observations, specific information and data from a site, etc.) from inspectors and industry about observed unintended consequences and whether these can be mitigated. Assessment: Examples of unintended consequences shared from FDA and Industry to determine if mitigation is needed. e. Harmonization Assessment: Are other regions requiring the submission or developing the submission of metric data. What efforts need to be addressed to harmonize metric reporting globally before FDA's program is used officially?	

General Comments	Rationale
It is suggested that this milestone evaluation be in the form of a public meeting to share FDA's assessment and industry's experience during this initial "assessment period", and determine whether any adjustments to theprogram are appropriate prior to full implementation into FDA's inspection risk-	
2. If FDA chooses to begin with a pilot, PDA supports applying this to sterile dosage forms.	Sterile dosage forms represent the highest risk and represent the largest number of drug shortages.
3. PDA realizes that the draft guidance document does not go into sufficient detail to properly assess and comment on issues regarding submission of metric data through ESG. PDA proposes that FDA make these details available through a separate document (the *Technical Conformance Guideline*, referenced by Ron Fitzmartin at the public meeting) for public comment so that PDA could provide its assessment and comment on the specific submittal details.	The PDA submittal team raised a number of concerns about submission of metric data through ESG. PDA understands that FDA is working on a technical compliance guide for submitting metrics. PDA recommends that FDA provide more details on submittals of metrics and allow the public to assess and comment on these details.
4. PDA suggests establishing a program that allows sites to update their metric data should errors be discovered after submission to FDA.	It is possible that errors in metrics data reporting may occur. Industry needs to understand FDA's expectations on the process for revising previously reported data.
5. PDA suggests that this new guidance document (the *Technical Conformance Guideline*, referenced by Ron Fitzmartin at the public meeting) clarify submission of metric data and include examples of completed data forms for multiple manufacturing sites.	These examples would provide Industry with additional clarity on FDA's expectations on how data should be structured and submitted.

6. PDA appreciates FDA's acknowledgement that quality culture, specifically senior management engagement, is important and its commitment to continue dialogue with the industry to discuss how it can be best measured and assessed.	
7. PDA urges FDA to utilize its risk-based inspection model beyond the routine inspections to include pre-approval inspections with the potential for fewer inspections at those sites deemed lower risk- based in this model. PDA also appreciates the agency's interest in considering these metrics for risk-based determination of the reporting category of post- approval changes.	Expanding the use of metrics and the risk-based inspection model into PAI inspections and post-approval change reporting would aid the FDA in further prioritization of scarce inspection and review resources, and provide additional incentive to firms to monitor, submit, and improve their metrics.
8. PDA understands FDA cannot be fully transparent in its inspectional risk-based model, but requests that sites be notified of their risk relative to the peer group.	Receiving feedback will provide sites with benchmarks to measure continuous improvement or even compare sites within their firm and across the Industry.
9. PDA recommends that reporting commence at least six months after the final guidance is available to allow industry to activate data compilation, analysis, governance and reporting processes on the final identified set of requested data.	Companies may not currently be collecting the data requested by FDA, at least not in a readily retrievable way, and they will need time to adjust their processes and systems.

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale
75-79, and 287	FDA may add to, revise, or remove quality metrics data from future quality metrics data requests to reflect our understanding of current manufacturing and establishment considerations and the utility of the data the Agency has received.	FDA may add to, revise, or remove quality metrics data from future quality metrics data requests through an update to the guidance document or other public comment process to reflect FDA's understanding of current manufacturing and establishment considerations, and the utility of the data the Agency has received.	PDA recommends clarifying this statement by adding "as applicable through updates to the guidance document and requests would not be made for additional metrics to individual companies or sites at any time without official FDA review process."

Line No.	Current Text	Proposed Change	Rationale
250-257	Under section 501(j) (added by FDASIA section 707), a drug is deemed adulterated if it has been manufactured, processed, packed, or held in a facility the owner of which delays, denies, or limits an inspection, or refuses to permit entry or inspection.[16] If an owner, operator, or agent of a facility fails to produce records and information requested pursuant to section 704(a)(4) of the FD&C Act within a reasonable timeframe, drugs from the facility may be deemed adulterated under section 501 of the Act and subject to enforcement action. Additionally, refusal to permit access to a record as required under section 704(a) of the FD&C Act is a prohibited act under section 301(e) of the Act.	Omit this language.	Quality metrics should be a means for incentivizing and improving quality, not a punitive measure. Currently, the FDA has numerous enforcement tools at their discretion to protect the public health, including conducting a For Cause cGMP Inspection.

Line No.	Current Text	Proposed Change	Rationale
276-284	"For example, is it more meaningful to compare metrics for different products within the same establishment, or for the same product manufactured at different establishments, or as an establishment-specific trend over time? Is it more appropriate to use certain metrics to compare all types of establishments (or a subset making the same dosage form or same drug) against each other? What is the best way to compare metrics for products that vary in manufacturing complexity (e.g., biotechnology and biological products are often considered more complex to manufacture)?"	PDA recommends that FDA remove these questions in the text and continue dialog with industry. It is better to have these questions addressed outside the guidance than provide these questions within the guidance document.	There is concern that investigators will not understand how to use the guidance questions and may make inappropriate comparisons and draw erroneous conclusions.
287-290	"FDA intends to carefully review data submitted in response to its requests,…We may add to, revise, or remove quality metrics data from future requests to reflect our understanding of current manufacturing and establishment considerations and the utility of the data the Agency has received."	We may add to, revise, or remove quality metrics data from future quality metrics data requests through an update to the guidance document or other public comment process to reflect our understanding of current …	Based on the current text in these sections, it is unclear whether FDA plans to use the guidance revision process to add new metric data requests.

Line No.	Current Text	Proposed Change	Rationale
320-322	In addition, products associated with an establishment that does not report as required under section 704(a)(4)(A) may be deemed adulterated under section 501 and subject to enforcement action.	Omit this language.	Quality metrics should be a means for incentivizing and improving quality, not a punitive measure. Currently, the FDA has numerous enforcement tools at their discretion to protect the public health, including conducting a For Cause cGMP Inspection.
Line 421		Lot Acceptance Rate = 1–X (X= the number of **specification**– related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe). For application products, specifications are those listed in the application. For non-application products, specifications are the companies' release criteria.	Clarification of the term "specification", so as not to discourage precautionary rejections for other reasons.

Line No.	Current Text	Proposed Change	Rationale
Line 425		Product Quality Complaint Rate = the number of product quality complaints received for the product divided by the number of individual units distributed containing drug product ~~by the total number of lots of the product released~~ in the same timeframe	PDA recommends individual units as a more accurate denominator because the lot size can fluctuate and patients can receive individual units. PDA also understands that the number of individual units may be challenging to calculate and recommends the concept of "patient unit" that would align with what a patient receives or what a pharmacist would dispense. Some example denominators: For parenteral products – patient unit = 1 vial or 1 syringe. For oral products, both Rx and OTC – patient unit = 100 tablets or 100 capsules. For inhaled products or liquids – patient unit = 1 bottle or 1 container. Note: Free text field can be used to explain changes in seasonal trends.

Line No.	Current Text	Proposed Change	Rationale
Line 429	Invalidated Out-of-Specification (OOS) Rate= the number of OOS test results for the finished product invalidated by the establishment divided by the total number of OOS tests results divided by the total number of tests performed by the establishment in the same timeframe.	Invalidated Out-of-Specification (OOS) Rate= the number of OOS test results for the finished product invalidated by the establishment divided by the total number of OOS tests results divided by the total number of tests performed on the finished product by the establishment in the same timeframe.	PDA recommends clarifying that the total number of tests in the denominator are only those tests for finished product and not raw material test or other analysis not directly related to the finish product testing.
Line 436		Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate= the number of APRs or PQRs completed within 30 days of annual due date established by the firm at the establishment divided by the number of APRs due in that same reporting period. ~~products produced at the establishment~~	PDA requests adding clarification that it is not necessary for the entire APR to be completed in 30 days but that the report must be completed within 30 days of the established internal due date.

Line No.	Current Text	Proposed Change	Rationale
Line 481	Proposed Optional Metric 2 What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?	What percentage of your corrective actions involved ~~re~~training of personnel as the only corrective action?	PDA feels that this metric might not achieve the desired objective, but if retained, PDA recommends Optional Metric #2 be modified slightly to focus on CAPAs that involve ~~re~~training as the only corrective action since most of the time, retraining would be required of most CAPAs as result of other corrective actions such as procedure revision or system changes.
Line 506	Proposed Optional Metric 3 A "yes" or "no" value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product's APR or PQR.26	PDA would propose a slight modification to this metric. PDA suggests adding the following to the end of the first question: A "yes" or "no" value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product's APR or PQR **for those critical quality attributes that lend themselves to statistical analysis.**	PDA supports this voluntary metric as it helps drive Industry toward process understanding and adopting continuous improvement efforts to reduce process variability. The validity of the analysis can be verified during inspection. Process capability or performance index calculations may not be appropriately applied to "each" CQA, such as sterility.

Line No.	Current Text	Proposed Change	Rationale
Line 535		The number of **specification**–related rejected lots in a timeframe divided by the number of lots attempted by the same establishment in the same timeframe). For application products, specifications are those listed in the application. For non-application products, specifications are the companies' release criteria.	This proposed change aligns with the comment on line 421 to include any quality related issues that lead to the rejection lots of product beyond just specification. In PDA's interpretation, media-fill failures would not be considered lots of product and would not be reported under this metric.
Line 538		**The number of attempted lots pending disposition for more than 30 days days past the longest time required to perform the longest assay. (unless the delay is pending application approval).**	For some product and process types, the normal cycle time may be significantly longer than 30 days and even as large as 120 days. This metric, as defined, would require reporting of many in-process lots. Alternatively, FDA may consider just counting all lots attempted, dispositioned (both released and rejected), and pending each quarter without the 30-day cut-off.

Line No.	Current Text	Proposed Change	Rationale
Line 552	If the associated APRs or PQRs were completed within 30 days of annual due date for the product.	~~If the associated~~ **The number of** APRs or PQRs ~~were~~ completed within 30 days of annual due date ~~for the product~~ **established by the firm.**	This clarifies the 30 days is after the firms established due date for the APR.
Line 555	The number of APRs or PQRs required for the product.	The number of APRs or PQRs ~~required for~~ **due within specified reporting period** ~~for the product~~.	This clarification is aligned with comments above on line 552. APR and PQRs would be for multiple products.
Line 700	New text to be added	Add the following sentence to the definition of OOS: **For the purpose of this guidance, OOS with inconclusive investigation (see FDA guidance on OOS), should be counted as confirmed OOS since inconclusive investigations would not be considered invalidated test results. For the purposes of this guidance, invalided OOS are those that become invalid as a result of confirmed lab errors.**	This change aligns with FDA OOS guidance and clarifies that only lab error invalids need to submit.