



PDA POINTS TO CONSIDER: Pharmaceutical Quality Metrics© 2013 PDA, Inc.

**PARENTERAL DRUG ASSOCIATION POINTS TO CONSIDER:
Pharmaceutical Quality Metrics**

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1.0 Introduction

1.1 Background

The 2012 Food Drug Administration Safety and Innovation Act (FDASIA) gave FDA new tools to encourage high quality manufacturing of pharmaceuticals and enhanced the agency's ability to respond to, prevent and mitigate the risk of drug shortages. Section 705 of the Act specifically requires FDA to implement a risk-based inspection regimen, while section 706 allows FDA to request, and firms to provide, records in advance of or in lieu of inspections. Early in 2013, FDA reached out to industry and the public for input into the use of quality metrics as a means to assist in the evaluation of product manufacturing quality aimed at predicting and preventing drug shortage issues and as a tool for use in the risk based inspectional model. In March 2013, PDA submitted a substantial response on behalf of its members and since that time has been an active participant in an ongoing dialogue with the agency culminating in the PDA Pharmaceutical Quality Metrics Conference held December 9-10, 2013 and co-chaired with the FDA. More than 300 conference participants representing 150 companies attended. The attendees represented a wide range of functional responsibilities including quality, engineering, manufacturing, technical services, and regulatory affairs. Virtually every sector of the industry, both overseas and domestic, was represented including generic, OTC, CMO, pharmaceutical, and biotech companies manufacturing large and small molecule APIs and drug products.

A PDA task force together with FDA staff planned the highly interactive conference maximizing the opportunities for dialog. In conjunction with the conference, additional PDA members began work on this Points to Consider document. PDA recognizes FDA's intent is to establish metrics with clinical relevance to patients which will also move towards a more proactive quality assessment model for companies. PDA also understands the objective is to move organizations from assessing primarily against compliance standards to assessment based on quality performance against established clinically-relevant specifications and driving continual improvement.

As discussed at the conference, the industry currently uses metrics to assess many aspects of their operations but most of the metrics being used are lagging indicators. Conference attendees recognized that in the future these metrics need to move towards being leading indicators. PDA asserts assessing trends is the best approach to take for leading indicator metrics and demonstrates a commitment to continuous improvement in line with ICH Q10 principles. The use of leading indicators is necessary to improve prediction and mitigation of potential drug shortages especially in increasingly complex manufacturing process and supply chain environments.

1.2 Purpose and Scope

The purpose of this document is to put forth the current thinking of the PDA membership based on various membership dialogs and the outcomes of the discussions held during the PDA Pharmaceutical Quality Metrics Conference. In general, PDA membership is supportive of FDA's efforts and appreciates that quality metrics are important tools that, if designed correctly, can be used to create a dialog to drive continuous improvement; to provide early detection of control drifts; to focus resources in a particular area; and to ensure a stable, long term supply of drug products to patients. The use of metrics in this



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manner will assist companies in moving to a performance-based culture. The attendees also recognized the culture of an organization is important to institute reliable, meaningful metrics while avoiding unintended consequences. Several elements needed for a culture that supports the use of metrics as a vehicle to continuous improvement were identified by the participants and include open and honest communication, clear vision of and belief in quality, management leadership and sponsorship of quality initiatives, listening, training and implementation of a team approach to continuous improvement. The attendees also agreed metrics to measure these attributes of a quality culture will be difficult to develop and report in the short term.

PDA acknowledges measuring quality needs a defined set of standards and requirements but one set of standardized metrics cannot act as a surrogate for quality. PDA recognizes the many benefits of metrics to enhance visibility and transparency between industry and regulatory authorities, to prioritize and focus on the most important issues, to elevate an organization's focus on quality, and to drive continuous improvement. PDA recommends that FDA choose metrics carefully, establish clear definitions, and be mindful of the cultural impacts of identifying and collecting quality metrics. PDA believes companies who demonstrate quality performance should be given an opportunity to fully realize their continuous improvement efforts by preferred handling of post approval change submissions that enhance their system and process capability. Additionally, such companies should receive less frequent inspections. Such preferred opportunities support the FDA's goal of a maximally efficient, agile, flexible, pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

This Points to Consider document provides the consolidated opinions and recommendations from PDA individual member scientists, who represent global perspectives in pharmaceutical, biological, and device manufacturing and quality. The positions expressed were developed by the task force and include input from the more than 300 Pharmaceutical Quality Metrics Conference attendees representing views from approximately 150 companies.



2.0 PDA Recommendations

The PDA proposal for quality metrics focuses on driving continuous improvement within a company and across the industry. PDA accepts the challenge to assist in identifying objective metrics that accurately indicate product and site health and avoid unintended consequences. PDA thinks quality metric data must consider three perspectives: patient, regulator, and manufacturer. PDA understands metrics are just one of a number of elements FDA will use for the overall evaluation of product quality, site operations quality, and site systems performance. PDA also acknowledges the list of metrics reported can expand or change over time as this new program matures and moves further into the use of leading metrics. Many factors must be balanced to achieve the aforementioned objectives including:

- Discussing quantitative (generally more objective) metrics vs. qualitative metrics (often with few shared definitions across industry) and developing common definitions;
- Discussing the difference between product specific vs. site and system quality metrics;
- Defining the difference between GMP metrics to indicate compliance with regulations vs. metrics beyond GMP which assess overall quality status of a site or product and the quality culture
- Identifying and defining leading metrics (generally harder to define but more useful) vs. lagging metrics
- Discussing the use of external (commonly understood and reportable to regulators) vs. internal metrics (defined by a company or site and used diagnostically)

PDA commits to working with FDA and to invite other industry associations to assist in developing harmonized definitions for metrics. PDA further commits to conduct a blinded survey and pilot collection program using the proposed metrics to identify issues and challenges that would need to be addressed during the roll out. The data from these activities will be used to help assess the robustness of the proposed definitions, the ease and ability in which the data is collected, and the knowledge and value gained from the data reported.

2.1 Recommended Metrics for FDA Collection

PDA recommends that FDA collect and assess trends of the product and site quality metrics listed below.

- Trend Metrics Collected per Product
 1. Confirmed Product Quality Complaint Rate by Product
 2. Batch Reject Rate by Product
 3. Confirmed OOS Rate (Drug Substance & Drug Product) by Product
- Trend Metrics Collected per Site
 1. Confirmed OOS Rate (Drug Substance & Drug Product) by Site
 2. Batch Reject Rate by Site

This recommendation is made after consideration of several possible metrics for product and site assessment, the need to avoid unintended consequences potentially resulting in drug shortages, and the



resource burden of reporting and analyzing metrics across the regulated industry. PDA further recommends companies provide the rate of occurrence, provide the numerators and denominators used for the calculation, and accompany their submissions with explanations or interpretations of actual numbers and trends. Because these are commonly tracked metrics in industry today, PDA believes reaching clear definitions in a relatively short period of time is achievable. While PDA recognizes these could be characterized as lagging indicators, trending these metrics, in many cases, may provide predictive and actionable information.

PDA has established a task force to develop definitions for the recommended metrics. Proposed definitions will be added in a future update of this paper. PDA recommends FDA take sufficient time to make sure definitions are accepted, well understood and the data collection process is well established before analysis and use in risk-based calculation begin. PDA suggests FDA avoid retrospective collection of data because it may not be available for some companies, may not be accurate based on new definitions, and may be highly resource consuming for both the agency and the industry.

2.2 Metrics Identified as Important but Difficult to Compare

Conference feedback identified the following metrics as being important and among the most difficult to make comparable for external reporting to the FDA. PDA is evaluating these in addition to the other metrics listed in the appendix to determine the feasibility of reaching common definitions and the ease of collecting and reporting the data to the FDA.

Quality Metrics by Product

- Process Capability (CpK, PpK, etc.) Rate

- Critical Investigations Rate

Quality Metrics by Site

- CAPA Effectiveness Rate

- Critical Investigations Rate

- Environmental Monitoring (excursions in A&B areas) Rate

PDA is focusing initial efforts on developing the Process Capability metric as a leading manufacturing performance indicator based on the output from the conference. PDA believes this metric is key to long-term continuous improvement of product quality across the industry. The conference attendees indicated reporting of this metric would require a phased approach and dialogue between industry and FDA.

2.3 Considerations for Comparing Metrics

PDA recommends the focus of the data collected should be on the trend and variability in metrics to drive continuous improvement. Comparing absolute values of metrics between products, sites and companies is difficult because of the variety of differences that could impact the applicability of the absolute value of metrics. The conclusion of the conference attendees was that trends were more reliable predictors of



potential risk than single values. For example, one site that produces complex dosage forms (e.g. pre-filled syringes) might be expected to have higher levels of critical investigations or deviations than a site producing traditional solid, oral dosage forms. Alternately, a product produced at high volume may have an overall percent of defects significantly less than the percent for a lower volume product but an increasing rate over time has greater potential risk to market supply. PDA recommends that adverse trends and variability in quality metrics trigger further discussion between FDA and the manufacturer or license holder while acknowledging the challenges of limited available resources for such discussions. The industry speakers at the Quality Metric conference reiterated the need to understand the “context of the metrics” to make proper use of metrics. Quality metrics should not be used as primary evidence of a GMP violation that would trigger regulatory action in lieu of such dialogue.

2.4 Benefits and Risks

FDA’s collection and utilization of quality metrics through the authority granted by FDASIA will create challenges for industry. The potential benefits should be balanced against the risks to ensure that together regulators and manufacturers select metrics that matter. Benefits to FDA and industry include:

- Greater visibility and transparency between industry and regulators allowing prioritization and focus on the most important issues and facilitating proactive discussion and action;
- The ability to identify drifts earlier, to drive audit and inspection schedules based on trends and possibly prevent problems and losses which could lead to drug shortages;
- Risk based approach to inspection of manufacturing sites thus freeing up resources to conduct other activities;
- Increasing consistency of metrics that are measured for products and sites across the industry by sharing of common definitions, leading to continuous improvement and a clear message that quality is everyone’s job.

The collection of metrics by FDA also poses significant risks to both FDA and industry including:

- Driving wrong behaviors which lead to unintended consequences in order to achieve the prescribed metrics target;
- Establishing excessive numbers of or overly complex metrics that take resources away from daily activities (both industry and FDA) impacting product delivery and quality;
- Comparing data that is not consistently defined or interpretation of single data values instead of aggregates and trends leading to wrong conclusions and responses;
- Using quality metrics as a quality surrogate resulting in inappropriate or over reactive responses to metrics without understanding the context surrounding the results.

3.0 Alternate Approaches

3.1 Direct Comparison Metrics

PDA acknowledges FDA has made specific requests for absolute value and trends of metrics appropriate for direct comparison between products and manufacturing sites. If FDA goes forward with direct comparison, PDA would suggest that this be limited to two product metrics and one site metric reported annually and recommends the following:



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- Confirmed Out of Specification (OOS) Rate for each product (including both drug substances and drug products), calculated as total number of confirmed OOS results per total number of specification tests
- Recall Rate by Product, calculated as number of recalls per total drug product lots (FDA would need to standardize the enumeration process for counting recalls.)
- OOS Rate by Site, calculated as the rate of confirmed OOS across all products produced at a manufacturing site

These are suggested as the only direct comparison metrics because there is already a common definition and understanding within the industry and their calculation is easily determined.

3.2 Benefits and Risks

In order for a direct comparison approach to be feasible, a clearly defined objective for the metric and industry wide agreement and understanding on the definition must be achieved. Failure to complete these important steps could lead to a divergence of interpretation across industry including some interpretations to make results appear in a more favorable light obscuring the true risks to product quality. PDA is concerned that using direct comparison of metrics could shift the focus to having the best metrics rather than having the best quality system and highest quality products.

4.0 Conclusions

PDA recommends a focus beyond just comparing numbers in order to achieve FDA's goal of objective measures of product quality, site operations quality, and site systems performance to assist in making risk based decisions such as inspection schedule, assessing drug shortage potential due to product quality problems, post market change reporting, and adding more structured elements to on-site inspections. With the principle of "first do no harm", FDA must do what it can to avoid unintended consequences of metrics collections. An additional risk to the program is the need to translate this new paradigm of quality into the current ORA inspectional approach. FDA should be clear its goal is not to receive "good" metrics numbers but to focus on what is best for quality and patients. FDA should limit the number and types of metrics collected to avoid the resources allocated to metrics collection at a firm taking away from resources for mitigation and prevention of risks to product quality and avoid a focus on certain specific metrics to the exclusion of a holistic quality systems approach. PDA recommends that FDA focus on longer term results and trends rather than snapshots of current numbers because the value of metrics is in driving continuous improvement over the lifecycle of a product which will drive value and benefit for industry, regulators and health care consumers. PDA acknowledges that additional work and dialogue is needed to develop clinically relevant product specifications that will provide transparency in assessing the health and quality of pharmaceuticals and the companies that manufacture them. PDA acknowledges that further work and discussion is needed to develop both the rate calculation and proper algorithm. PDA welcomes involvement with FDA and from other organizations in the establishment of a pilot program to move this program to the feasibility stage and begin assessing and verifying the collection of a small set of metrics to ensure success of the program and prevent unintended consequences.



5.0 Appendices

5.1 Definitions

PDA has established a task force to develop definitions for the recommended metrics. Proposed definitions will be added in a future update of this paper.

5.2 Other Potential Metrics Considered

During discussions of the development of this Points to Consider document and during the break out sessions at the December 2013 conference, PDA evaluated many possible metrics. All of these are appropriate for internal use by individual companies and sites to evaluate the quality and reliability of their own manufacturing processes. However, at this time PDA feels these would be overly difficult for use as external metrics to be compared across multiple companies and products because of the degree of interpretation and discussion needed to achieve common definitions. Many of these are subjective and therefore could lead to pressure on manufacturing and quality staff to report “the best” numbers rather than a focus on improving overall site and product quality. PDA recommends these types of metrics are most appropriate for use in the context of a healthy quality system and quality culture where the focus is not on comparing numbers but understanding the indicators of potential risks and identifying the appropriate mitigating actions.

- Other Potential Product Metrics Considered
 1. Adverse Event Rate (difficult to correlate to specific lots, quality issues and specific drug product)
 2. Batch Failure Rate
 3. Confirmed OOT Rates
 4. Deviations Rate
 5. Batch Yields Rate
 6. Major Change Initiated
 7. Potential Stock-out or Drug Shortage Rate
 8. Recall Rate
 9. Repeat CAPA Rate
 10. Distribution Excursion Rate (unfulfilled requests)
 11. Right the First Time Rate

- Other Potential Site Metrics Considered
 1. Confirmed OOT Rates by site (exceeding an action level)
 2. Deviations Rate
 3. Environmental Monitoring Excursions Grade A & B areas Rate



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4. PIC/S Inspection Scoring. Number of PIC/S member inspections and number of critical & major observations
5. Training Effectiveness / On-time Completion Rate
6. Percentage of Overdue PM for Critical Equipment Rate
7. Unplanned Downtime Rate-- because of unplanned maintenance including utility failures
8. “Right First Time” Rate
9. Reject Rate (partial vs. full rejects, API vs. DP)
10. Analytical invalid Rate
11. Contamination Rate
12. Recapitalization as % of the Asset Value Rate
13. PM as % of Asset Value Rate
14. Audit / Inspectional Commitment On-Time Completion Dates Rate
15. Organizational Health Metric (percentage of temporary workforce, employee satisfaction %, safety, employee turnover rate)
16. Risk Management & Mitigation Profile Changes
17. Cycle Times (disposition and end to end) Rate
18. Human Error Rates
19. On-time Annual Product Review
20. Repeat Deviations Rate
21. Investigation Free Lots Rate
22. Potential Stock-outs or Drug Shortages Rate