QUALITY METRICS: ADEPTNESS PROVOKING PRACTICE

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ABSTRACT

Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be used by FDA to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers to improve the Agency’s ability to predict, and therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing. This article includes an explanation of how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to collect data and use quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry to help move towards a desire state and Path to achieve regulatory flexibility and reduced post market change control burden.

KEYWORDS: Quality metrics, Risk Management, Quality, Manufacturing, Post Market.

INTRODUCTION

The 2012 Food Drug Administration Safety and Innovation Act (FDASIA) gave U.S Food and Drug Administration 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. Have initiated a comprehensive new organization of its inspection activities. One of the key elements of this initiative is the Quality Metrics Program. This program will throw a complete new light on the compliance status of each manufacturing site. So far there were only two categories: GMP compliance or non-compliance. There was
no benefit for industry to improve the overall quality as long as the manufacturing site was rated to be in GMP compliance.

The chances have been good that a non-compliance situation would not be discovered by FDA inspectors. The frequency of inspections - especially those in foreign countries - was not meeting internal FDA standards. Instead of inspections at least every two years, some facilities have not been inspected for a long period of time and thus have developed a "culture of non-compliance". When they finally were inspected, some major GMP deviations were discovered and caused comprehensive compliance actions such as FDA Warning Letters and Import Alerts. This has resulted in some serious drug shortages because medicinal products were only manufactured at very few manufacturing sites. The FDA Quality Metrics initiative aims at asking each production site (APIs, medicinal products, Biotech, OTC etc.) to provide data about the "quality level" in the manufacturing site. By this, FDA will be able to see from the data how well the quality system is maintained and how successful the quality system will affect the quality of the medicinal products.

In July 2015, after years of discussions, FDA released its draft guidance, Request for Quality Metrics, explaining the agency's general approach to quality metrics and requesting industry input on certain areas still being considered by the agency.

FDA said it plans to ask manufacturers for certain quality metrics to "improve the efficiency and effectiveness" of its inspections, claiming the information could be used "to reduce the inspection frequency at an establishment."

FDA said its authority under section 704(a) (4) (A) of the Food, Drug, and Cosmetic Act to collect records "in advance of or in lieu of" an inspection provides the agency with a legal basis to request quality metrics from companies.

Goals of quality metrics

1. Responsibilities for setting up the measurement of what is actually taking place with respect to quality.
2. Responsibilities for reviewing result against goals and for taking action on significant variation.
3. Path to achieve regulatory flexibility and reduced post market change control burden.

Background[8,9]
FDA’s approach to quality oversight has evolved in recent years. CDER and CBER are committed to supporting the modernization of pharmaceutical manufacturing as part of the Agency’s mission to protect and promote public health. These efforts also may be one long-term strategy to mitigate drug shortages by addressing underlying causes of shortages, as noted in FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages. In 2002, FDA launched an initiative entitled “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach,” to encourage the implementation of a modern, risk-based pharmaceutical quality assessment system. The initiative was published with several goals, including ensuring that regulatory review, compliance, and inspection policies continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry. Since publication of the Pharmaceutical cGMPs for the 21st Century, CDER has promoted a vision of quality matrices. Quality matrices is defined as “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight”(5).

There have many guidelines issued by FDA and by the international conference on harmonization (ICH) Q8, Q9, Q10; Q11 which have provided a regulation to move towards desire state.

**Criteria to select the quality metrics**[10,11]

FDA used the following criteria to select the quality metrics that it intends to calculate using requested data when this guidance is final: metrics should be

1. Objective,
2. Subject to inspection under section 704 of the FD&C Act, and
3. Valuable in assessing the overall state of quality of the product and process, commitment to quality by the manufacturer, and the health (i.e., effective functioning) of the associated PQS, while
4. Avoiding any undue reporting burden.

These metrics are not intended to be an all-inclusive set of the quality metrics that FDA 106 could consider useful to assess a product and manufacturer’s state of quality.

**Use of Quality Metrics by FDA for Risk-Based Inspection Scheduling and Prediction of Drug Shortages**
The quality metrics program is expected to play an important role in addressing risk-based inspection scheduling and in the prediction, and potential mitigation, of drug shortages. Section 510(h)(3) of the FD&C Act was amended by section 705 of FDASIA to require that FDA inspect establishments that are required to register with FDA “that are engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs in accordance with a risk-based schedule established by” FDA. The provision replaced the requirement that FDA conduct inspections of certain domestic drug establishments at least once every two years. Risk-based scheduling helps FDA focus resources on facilities that present the greatest risk to consumers.

These risks are based on certain factors as outlined in section 510(h)(4)(A-F).

(1) The compliance history of the establishment;
(2) The record, history, and nature of recalls linked to the establishment;
(3) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment;
(4) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years;
(5) Whether the establishment has been inspected by a foreign government or agency of a foreign government recognized under section 809 of the FD&C Act; and,
(6) Any other criteria that FDA deems necessary and appropriate for purposes of allocating inspection resources.

The collection of these data is also intended to help direct our inspections. In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes, with emphasis on encouraging lifecycle manufacturing improvement. However, if the integrity or utility of the quality data submitted is found questionable based on FDA’s evaluation of submitted data or other information, such as an on-site inspection, the uses to which we would put the reported quality data would need to be re-evaluated, along with the nature of future requests.

How FDA Intends to Use Quality Metrics[11]
FDA intends to use quality metrics data to further develop FDA’s risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to improve the efficiency and effectiveness of establishment inspections, and to improve FDA’s evaluation of drug manufacturing and control operations. FDA expects that the initial use of the metrics will be to consider a decreased surveillance inspection frequency for certain establishments. FDA intends to evaluate whether data reported by manufacturers is consistent with the Agency’s understanding of the specific quality data requested (e.g., definitions). In addition, we intend to evaluate how best to in FDA intends to carefully review data submitted in response to its requests, to help inform decisions about additional quality metrics data requests the Agency may make in the future. 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 also intend to provide additional opportunity after our initial requests are made for industry to provide feedback and additional comments, as well as share knowledge from ongoing quality metrics programs. FDA recognizes that any individual data point or quality metric is not solely indicative of the state of quality of the establishment or products; rather, FDA intends to use this information in context. For example, the use of new, in-line analytical technology used for real time release testing with increased sensitivity might result in better detection of in-process out of specification (OOS) results and a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will allow for improved assurance of quality. FDA is sensitive to this possibility and continues to support and encourage the use of modern manufacturing technology. FDA also intends to use quality data collected under section 704(a)(4)(A) of the FD&C Act as one factor in identifying establishments that may pose significant risks to consumers, such as risks from unsafe products and drug shortages. Reported data and metrics, along with internal FDA data (e.g., inspection results, recalls, Field Alert Reports, Biological Product Deviation Reports) may indicate an ongoing product quality problem that requires correction. Evaluation expert and use the metrics.

**Who reports and who may contribute to the report**

The owners or operators of establishments that are engaged in the manufacture, preparation, propagation, compounding, or processing of a drug are required to report data to FDA that the Agency may inspect under section of the FD&C Act, upon the Agency’s request, in advance or in lieu of an inspection. FDA intends to give notice in the Federal Register to
certain owners and operators of establishment subject to inspection under section 704 that they are requested to submit quality metrics data.

**Effects of Non-Reporting**
The failure to report requested quality data may elevate an establishment’s predicted risk in FDA’s prioritization of inspections and may lead to an earlier inspection. 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.

**Quality Metrics that FDA Intends to Calculate**[^12,^13]
The following set of quality metrics that FDA intends to calculate based on industry reporting was developed with stakeholder input. The metrics were identified as being objective, subject to inspection under section 704 of the FD&C Act, and a valuable component in assessing the overall effectiveness of a PQS, within reasonable limits, and in a reasonable manner, while avoiding an undue reporting burden. FDA believes that these quality metrics, in conjunction with other data accessible to FDA, provide important information about operational reliability and quality culture. Additional, optional metrics, as described below, could provide further detail about quality culture and process capability/performance. In this draft guidance, FDA seeks comment on whether to include the option of submitting these metrics when the guidance is final.

Using reported data described in the following section, FDA intends to calculate the following quality metrics for each product and establishment, where applicable.

1. **Lot Acceptance Rate:** \(1 - \frac{x}{n}\) (\(x\) = 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).

   Specification-Related Rejected Lot A lot that was rejected because it failed to meet at least one specification
   
   Lot Attempted A lot intended for commercial use for which the manufacturer has issued a lot number and charged API (for finished drug manufacturers) or primary starting materials (for API manufacturers).

2. **Right First Time Rate:** \(1 - \frac{1}{n}\) (the number of lots with at least one deviation by the establishment in a year divided by the number of lots attempted by the same establishment in the same year).
3. **Product Quality Complaint Rate**: The number of product quality complaints received for the product divided by the total number of lots of the product released in the same timeframe.

4. **Product Quality Complaint**: A complaint involving any possible, including actual, failure of a drug product to meet any of its specifications designed to ensure that any drug products conform to appropriate standards of identity strength, quality, and purity.

5. **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 test results divided by the total number of tests performed by the establishment in the same timeframe.

   Out-of-Specification (OOS) Result All test results that fall outside the specifications or acceptance criteria established in drug applications, drug master file, official compendia, or by the manufacturer. For the purpose of this guidance, this includes: (1) finished product and stability test results only and, (2) all finished product and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

6. **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 at the establishment divided by the number of products produced at the establishment.

What Kinds of Data would be reported?[^14,^15]

While many companies use specific quality metrics internally, there are no standards for what metrics are measured.

To begin, FDA has released a list of 10 baseline quality metrics it is considering, including metrics such as:

1. The number of lots attempted of the product.
2. The number of specification-related rejected lots of the product, rejected during or after manufacturing.
3. The number of attempted lots pending disposition for more than 30 days.
4. The number of out-of-specification (OOS) results for the product, including stability testing.
5. The number of lot release and stability tests conducted for the product.
6. The number of OOS results for lot release and stability tests for the product which are invalidated due to lab error.
7. The number of product quality complaints received for the product.
8. The number of lots attempted which are released for distribution or for the next stage of manufacturing the product.
9. If the associated annual product reviews (APRs) or product quality reviews (PQRs) were completed within 30 days of annual due date for the product.
10. The number of APRs or PQRs required for the product.

The agency is also asking for input on five "additional, optional metrics as evidence of manufacturing robustness and a commitment to quality."

1. Senior Management Engagement—was each APR or PQR reviewed and approved by the following: (1) The head of the quality unit, (2) the head of the operations unit, (3) both, or (4) neither?
2. Corrective Action and Preventive Action (CAPA) Effectiveness—What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?
3. Process Capability/Performance—A “yes” or “no” value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute as part of that product's APR or PQR.
4. Process Capability/Performance—A “yes” or “no” value of whether the establishment's management has a policy of requiring a CAPA at some lower process capability or performance index.
5. Process Capability/Performance—if “yes” to the previous question—What is the process capability or performance index that triggers a CAPA? If “no” to the previous question—please do not respond.

**How to Report Quality Data to FDA**

FDA intends to request that reporting establishments submit quality metrics data reports for a one-year period that begins after the Agency issues its requests, as specified in the request. Reports would be submitted within 60 days of the end date of the reporting period. For example, if the requests called data for the period October 1, 2016 to September 30, 2017, data reports would be due by December 1, 2017. We intend to request data segregated in the
report on a quarterly basis. Appendix A is a quality component list that describes the information that would be submitted to FDA through the FDA Electronic Submissions Gateway (ESG). FDA intends to provide additional technical details in a separate technical specification. Once FDA receives information in response to requests under section 704(a) (4), the Agency intends to issue a confirmation of receipt, in accordance with section 704(a) (4) (B) of the FD&C Act. Any optional metrics would may be submitted using the same method described above. Information included in quality metric data submissions should be submitted in English. FDA believes that segregating reports by quarter and the submission through the ESG on the timetable provided is within reasonable limits and in a reasonable manner.

**Key points for quality metrics**\(^{[15]}\)

1. Keep it simple
2. Improve the objectivity
3. Potential for regular flexibility
4. Build consensus
5. Promote the right behaviors (design metrics carefully to avoid unintended consensus)

**CONCLUSIONS**

Quality Metrics play an important role in the desired state of pharmaceutical quality and regulation. Induce the right behavior and responsibility for industry. Identify and reward firms going above and beyond. Potential to improve the efficiency and effectiveness of establishment inspections. Help to identify situations in which there may be a risk for drug supply and disruption Consider whether metrics may provide a basis to assist in determining the appropriate reporting category for post-approval manufacturing changes.

A robust quality metrics program requires continual improvement Ideal metrics is not limited to the metrics in this draft guidance Ideal metrics is specific to the product, site, and supply chain.

There are many issue and challenges to develop a quality metrics which are acceptable to both industry and regulators. The implementation of programs like quality metrics moves us closer to realizing the vision of the Pharmaceutical Quality for the 21st Century Initiative.

**REFERENCES**
1. Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration


