Patheon
Performance the World Over

Meaningful Metrics – A CMO Perspective

Metrics can be powerful tools to significantly boost a company's quality, performance, and success in the industry – when effectively created and utilized. Although metrics are an integral part of most pharmaceutical companies and outsourcing organizations, their potential can be accelerated when senior management and staff are fully supportive and actively involved in monitoring and implementing mitigation plans when needed. Current regulatory and industry publications suggest that regulatory agencies are giving greater attention to metrics as a way to quickly gauge site performance and commitment to maintaining or improving product quality, manufacturing capability and overall performance. This paper discusses the roles of sponsors and their contract manufacturing organization (CMO) partners regarding metrics, what metrics to measure, how to manage data, effective communications and ownership, and ways to improve your metrics.

Why Utilize Metrics?

Metrics are a standard of measurement by which the efficiency, performance, progress, or quality of a plan, process, or product can be assessed.[1] They are an objective measure of the quality of a product or process, the quality of a site, and the effectiveness of systems associated with the manufacture of products, including the pharmaceutical quality systems.

A quality metric, a measurement of quality, can be either a leading or lagging indicator. As an indicator of trends, a leading indicator is predictive, providing information proactively, rather than reactively, in order to anticipate a problem and take action before contravening a target or goal. A lagging indicator measures performance after the fact and can be used to determine if goals and objectives have been achieved.

Metrics provide feedback and information on a company's state of control, allowing you to make informed decisions. What is measured, assessed, and reviewed with management affects decisions, allocation of resources, capital investment and expense budgets. With clear, specific targets, metrics drive improvement, identify potential issues for early remediation, and are effective motivators. Simply put, metrics are good business.

What Are the Right Metrics?

To optimize the value of metrics, it is important to provide the right metrics to the right people in the right format. Keep them simple but specific, have defined terms, and collect a limited quantity, typically only those necessary to drive product and site improvement. Metrics should be time-related to be comparative (before compared to after the improvement is made) and have direction and scale. It is best to look at leading rather than lagging indicators, which enable you to be predictive rather than reactive.

When metrics are established and utilized properly, manufacturing data can become actionable, driving quality and performance improvements forward.

Common industry metrics include number of deviations (trending the root cause), deviations per batch, confirmed number of out-of-specification (OOS)/laboratory failure rates (trending the root cause), right the first time, and batch failure rate. Alternatively, another way to look at deviations is to track "deviations past due." This ensures that difficult investigations or investigations that are lagging behind get the attention they deserve to facilitate timely closure. This also mitigates risk of recurrence. However, completing an investigation (root cause analysis, Corrective and Preventive Action [CAPA] plan and approvals) in a timely manner is important, and ensuring the content of the investigation is complete and thorough is critical. This approach can also be applied for CAPAs. For "CAPA past due," keeping track of your CAPAs is imperative, but make sure timelines are realistic and there is a means to determine the CAPA's effectiveness. Some deviations and CAPAs may go past the due date for QA approval, but this should be the exception. Avoid giving extensions as this may remove the focus and drive to get it done.

Other considerations for metrics include: stability past due (compliance to pull dates), Annual Product Review (APR) past due (compliance to schedule, ensuring contractor portion is defined), SOP training compliance and environmental monitoring results, and trends and documentation errors.

The most important consideration is choosing the right metric for the site and challenging and re-evaluating it on a regular basis. Keep in mind that the intent of measuring is to drive continuous improvement and thus improved performance. If you routinely achieve 100 percent, then consider switching to another metric.

As noted earlier, the regulatory agencies are taking note of what sites are measuring and are looking to establish their own set of metrics to obtain from industry. Supporting the FDA's effort to establish industry-wide quality metrics, more than 300 drug maker quality representatives recommended the following top ten product and site quality metrics the FDA should consider collecting from manufacturers:[2]

- Confirmed product quality complaint rate
- Confirmed out-of-specification (OOS) or laboratory failure rate for a product
- Process capability by product
- Critical investigation rate of the product
- Batch rejection rate
- Effectiveness of the CAPA system
- Critical investigation rate by site
- Batch failure rates for the site
- Confirmed OOS rates by site
- Number of investigation-free lots
- Regardless of the metric, visibility of the measure throughout the organization and strong management, oversight and ownership are key to obtaining the true benefit for your efforts.

Effective Use of Metrics

The old adage, "What gets measured gets done," remains true, but sometimes we lose sight of why we collect metrics or question the value of what we are measuring. Only measure the metrics you want to improve – such as for service or quality, utilizing leading indicators when possible, rather than lagging indicators – and consider them from both product quality and GMP perspectives.

When preparing and utilizing a metric, we advise following seven steps:

1. Define the objective. State what you are measuring, how and how frequently you collect and measure data, goals, who is responsible for gathering the data, how they are recorded and when they are reviewed.
2. Define the metric – ensure that there is a clear understanding of the definition.
3. Set targets.
4. Collect data.
5. Assess the data in a timely manner and communicate the status internally and between sponsor and contract service provider. Keep in mind that what the sponsor measures may not be considered an important measure at the contractor's site.
6. Modify or change metrics according to the data.
7. If the target is easily achieved, raise the bar.

Formatting Metrics

Ideally a company should have its operational and quality information readily available in the right format for easy analysis and reporting. To make the data meaningful, define what constitutes a positive or negative trend, select reasonable scales and be consistent. For consistency,

the data entered should be normalized for field names, content scope, date range, procedural differences and requirement differences. Be sure to communicate and reinforce definitions and associated calculations.

For optimal efficiency and comprehension of data, automate metrics formatting as much as possible, eliminating subjectivity, and include colors to emphasize the good, the bad and the ugly. It is a good idea to include commentary to clarify anomalies or explain negative trends.

Data Management and Communication

For effective management and meaningful use of data, consider the following questions:

- How is the data reviewed, analyzed and assessed? If it stopped coming, would anyone know?
- Who sees the data? Is its visibility limited to Quality management?
- Is there open discussion?
- Is the data defined and understood? Does the internal management team understand what is being measured? Do the client and CMO have the same level of understanding?
- How effectively is the data communicated: Is it disseminated down to those who have an opportunity to influence or impact the outcome?

It is critical that results are effectively communicated and understood throughout the organization, with departmental ownership for their own performance metrics. Quality metrics do not only belong to the quality assurance department. A well managed department will be actively involved with the collection and dissemination of metrics pertaining to its area of operation and have detailed plans in place for remediation when deviations or negative trends occur. The metric result should never be a surprise to a well managed department.

Metrics should be reviewed at various levels so that all employees involved in the sponsor's program are engaged. They should be discussed at department and site management meetings, and reviewed by senior management. A metrics review meeting requires decisions and action plans. Employees should contribute to the CAPA plan and be acknowledged or rewarded for success.

At the site level, during the data review, each concern presented should have a defined CAPA plan. Site managers should be held accountable for remedying concerns, making improvements, and setting new or higher targets to bring about a positive change.

Senior management awareness, understanding and engagement are critical for project and overall business improvement. Executives should review and discuss the data during executive reviews, attend department or site level meetings periodically, and ensure sites are held accountable for remedying issues using a defined CAPA plan. Management should also provide the resources and capital necessary to rectify issues as warranted.

Managing Metrics With Your CMO

A CMO is an extension of a sponsor's operation. As sponsors are increasingly placing greater responsibility for quality and compliance on their outsourcing partners, they are also increasingly being held ultimately responsible by regulatory agencies for issues that may occur.

Sharing metrics and action plans for continuous improvements through CAPA should begin as early as the due diligence process when engaging the services of a CMO. Discussing metrics at the outset helps ensure that the right metrics will be evaluated. While each partner will have internal metrics, together they must set metrics for the sponsor's program and understand the terms and definitions. Additional operational and quality metrics, typically with less detail, are set at the site level and shared by both partners. However, the sponsor should recognize that the CMO has its own metrics program based on its need and limit, imposing additional metrics that may not be of value to the sponsor's operation.

Any current or potential critical issue related to the sponsor's product or a process should be shared between partners immediately, so that they can quickly react before the problem escalates. Both parties should have procedures in place for quickly communicating with each other about deviations, complaints, investigation results and corrective actions.

At the outset of the partnership, discuss how communications will take place between sponsor and contractor, as well as the internal communication among the contractor's multiple sites. Transfer of information and knowledge is an important first step that must be followed by open, effective channels of communication. This is important for processes such as complaint handling and change control. Communication systems should incorporate a quality

agreement for proper responsibility and accountability. Partners should also have current data-sharing systems and periodic meetings and reviews.

Patheon's Approach: Effectively Managing Metrics

Patheon, a global contract development and manufacturing organization (CDMO), adopts metrics throughout the organization to drive improvement. Metrics are aligned with our corporate objectives. We frequently and regularly assess the metrics we choose and how the organization has accepted them.

Jim Mullen, our CEO, and other senior management set performance improvement expectations for our sites. When sites achieve the targets, the bar may be raised.

While Patheon and our clients set metrics together, we often set ours higher to exceed client expectations. Cross-functional management teams review critical site quality and operation metrics on a frequent basis, acting on opportunities for improvement with site owners and taking steps to mitigate risk.

Internally, Patheon holds weekly meetings with site quality department heads and senior quality assurance management to review performance. Site-specific meetings are held if necessary to do a deeper dive to ensure that site personnel have what they need to drive quality performance forward. Monthly reports are also prepared and vetted by site leadership and senior management. To support corrections and improvement, Patheon provides additional resources and support as required. We meet regularly with clients to discuss quality and operational business, review the metrics and CAPA status, and suggest further improvements.

At Patheon, acting proactively to prevent or resolve problems and improve performance has a high priority. We trend and openly communicate deviations and root causes. When issues arise, we make sure corrective action is systemic across the organization. It is no coincidence that the best performing Patheon sites in Quality are also the best financially performing sites, and where quality lags, so do the financials.

Regulatory Guidance

GMP and regulatory guidance on what constitutes quality metrics is limited. In 2013, FDA published draft guidance on manufacturing Quality Agreements between a sponsor and CMO. The guidance expands on current guidance in ICH Q7, Q9 and Q10 that recommend supplier quality agreements, effective oversight and monitoring of outsourced operations. ICH Q7 advises drug manufacturers to establish formal agreements with their contractors on cGMP responsibilities. ICH Q10 clarifies that the sponsor bears ultimate responsibility for outsourced activities and for the quality of the product. In this guidance, performance indicators are described as "Measurable values used to quantify quality objectives to reflect the performance of an organization, process or system, also known as 'performance metrics' in some regions."[3]

Other references to quality metrics include:

- C.02.11 Canadian GMP requirements and 21CFR180(e) refers to APRs.
- U.S. GMPs refers to APRs.
- 21CFR820.20 - U.S. GMPs for Medical Devices refers to quality data.
- EU GMPs – Quality Management refers to product quality reviews.

To establish a more informative drug quality data analysis system and develop guidance on quality metrics, FDA is collecting quality metrics data from the industry. FDA hopes to define initial metrics by the end of 2014.

Five Keys to More Meaningful Metrics

In conclusion, whether you partner with a contractor or not, following these five suggestions will turn your metrics into actionable results that can enable you to achieve greater productivity and success for your business:

Collect the most meaningful metrics. Sponsor and contractor must define and agree on the metrics.

1. Choose a manageable quantity of metrics, only in the areas you want to focus on.
2. Select leading rather than lagging indicators, enabling you to be proactive in remediation.
3. Think forward, anticipating next steps to ensure continuous improvement.
4. Assess the data in a timely manner and regularly communicate the status internally and between sponsor and contract service provider.
5. Act on deviations and opportunities, utilizing an efficient, effective CAPA system.

References

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