

ISPE Comments on Food and Drug Administration Quality Metrics Reporting Program; Establishment of a Public Docket; Request for Comments [Docket No. FDA-2022-N-0075]

1. Balance of Quality Metrics and Quality Management Maturity

To meet FDA's vision of Pharmaceutical Quality for the 21st Century initiative of a "maximally efficient, agile, flexible pharmaceutical manufacturing sector that can reliably produce high-quality drugs without extensive regulatory oversight," ISPE believes there should be a balance of benefit to burden for both industry and regulators.

ISPE recommends that FDA increase engagement with industry representatives regarding the future direction of the FDA Quality Metrics Program. The current approach of issuing guidance, piloting programs, commenting on docket requests, and responding to polls during FDA conferences provides limited opportunity for dialogue. Expertise that all parties could provide to develop this important initiative could be better leveraged. ISPE was very encouraged by the collaborative nature of the Case for Quality Program within CDRH which utilized expertise of industry, academia, third parties, and FDA to create a robust, program that benefits all parties.

ISPE suggests the following be considered for a robust Quality Metrics Program:

- ISPE recommends that FDA consider where complementary programs or pieces of the same could be combined for a more simplified approach in the design of the QM Program including Quality Management Maturity (QMM), Case for Quality, Cares Act Reporting, etc.
- ISPE has a robust QMM program and is provided in [Appendix 1](#) for reference. This program was initiated in 2018 and is anticipated for completion by year end.
- Consider an initial voluntary phased approach to inform an expanded program.

ISPE envisions that a successful and valuable FDA QM program will include a well laid-out design explaining what/how the program will benefit industry and drive continual improvement. We recognize the challenges and complexity with respect to industry benefit/value and have summarized the following key suggestions for potential benefits:

- Pre-announced inspections
- Reduced inspection frequency
- Further reliance on other Agency inspections
- Adapt remote inspection models (Remote Interactive Evaluations, Use of Remote Interactive Technologies) to assist with assessment activities in lieu of physical inspections)
- Improved effectiveness/efficiency of inspections (resulting in shorter duration)
- Waiving of PAIs

ISPE suggests that increased clarity and transparency on potential benefits to industry would be welcomed by industry, for example:

- How reported metrics could lead to less frequent and reduced length of inspections.
- If and how reported metrics could provide a basis for "...FDA to use improved risk-based principles to determine the appropriate reporting category for post approval manufacturing changes" as indicated in the 2015 FRN, [Docket No. FDA-2014-D-2537] *Request for Quality Metrics; Notice of Draft Guidance Availability and Public Meeting; Request for Comments.*
- More thought might be given to incentives for the CDMO industry as the current proposed incentives are not easily applicable to this sector of the industry.
- Benefits to patients also should be identified and explained. For example, more clarity and analysis would be welcome showing how any one or a combination of the proposed reported quality metrics could assist with prediction of potential drug shortages. Industry adaptation of Quality Risk Management as in the most recent Risk Management Plan draft guidance¹ may provide an appropriate model.

ISPE suggests that additional consideration be given to potentially burdensome aspects of the Quality Metrics Program including data collection, calculation, reporting, changes in business conditions, and change management processes to update metrics definitions, reports, calculations, submitted information, etc. to ensure accuracy and transparency.

2. Proposed Practice Areas and Metrics

Background

ISPE recommended to its members that answers to the questions in the FDA Request for Comments be submitted directly to FDA by their companies, especially any companies that did not participate in the FDA pilot programs. In developing the feedback contained within this document, ISPE solicited input from its members via a survey containing specific questions relating to a QM Reporting Program. The results of that survey represent feedback received from twenty companies and is summarized in the following sections. ISPE is happy to make the full survey results available to FDA upon request.

Metrics Recommendations

Given feedback from the recent survey and based upon the output from ISPE QM Pilot Programs, Wave 1² and Wave 2³, ISPE recommends that a single metric, Deviation Rate, is considered and tested against some hypotheses. In Wave 1 and Wave 2, QM Pilot

¹ Risk Management Plans to Mitigate the Potential for Drug Shortages draft guidance, May 2022.
<https://www.fda.gov/media/158487/download>

² ISPE Quality Metrics Initiative: Wave 1 Report, <https://ispe.org/publications/guidance-documents/ispe-quality-metrics-initiative-wave-1-report>

³ ISPE Quality Metrics Initiative: Wave 2 Report, <https://ispe.org/publications/guidance-documents/ispe-quality-metrics-initiative-wave-2-report>

Programs Deviation Rate and Repeat Deviation Rate had relationships with external quality outcomes, LAR, and culture. Such an approach would have benefits of being voluntary, relatively simple and include the potential to be very informative

Supply Chain Robustness

ISPE recommends deletion of the Supply Chain Robustness practice area since it does not align with the objectives of a quality metrics program. The metrics proposed may be relevant to business performance for some companies, however, there was not a high level of support for these metrics in our survey with many strong comments that they were out of scope of a quality metrics reporting program. Additionally, there are issues with proposed metrics definition and calculation. For example, demand and orders may not be precise numbers, and Fill Rate, On-Time In-Full, Days of Inventory on Hand may be relevant to a distribution center not a covered establishment for some companies. Further, within several industry sectors, product fill rates are established by the customers or retailers. Supply Chain measures could and would provide unintended negative consequences in industry and should not be considered nor compared within a Quality Metrics program. Much resource and management attention would have to be given to explain data.

The proposed Supply Chain metrics are lagging indicators. Supply Chain metrics may include drivers that are outside of the control of pharmaceutical manufacturers, such as those influencing the supply chain during Covid-19, e.g., tankers unable to be unloaded or lack of truck drivers to deliver finished product to customers. Such metrics may be appropriate to consider in a QMM assessment program.

Manufacturing Process Performance

In our survey, support for reporting process capability values was polarized roughly equally between those for and against and, therefore, ISPE cannot recommend inclusion of this metric. This polarization may be due to number of batches manufactured within a reporting period, which may be insufficient to support calculation of process performance as well as the variable and inconsistent setting of specification acceptance criteria. Additionally, process capability may be measured by different means (e.g., Cpk, Ppk) and may have unique target ranges (1.0 or 1.33) based upon a product or process.

ISPE recommends that lot acceptance rate (LAR) is removed from the list of potential metrics since FDA has identified that it is not a discerning metric.

Lot release cycle time was not supported as a reportable metric in our survey

PQS Effectiveness

CAPA Effectiveness and Repeat Deviation Rate were metrics that companies generally considered useful internally to an organization, but often have very different definitions between products, business segments, and sites. Inclusion of metrics related to equipment

performance and Change Control Effectiveness was not supported by the survey respondents.

Laboratory Performance

ISPE recommends that any consideration for laboratory performance metrics fall within Manufacturing Process Performance as the Laboratory is a significant component of the overall Manufacturing Value Stream. The lab provides measures for the product at various points in the manufacturing process.

ISPE recommends that Invalidated/overtaken out-of-specification rate (IOOSR) metric is removed from the list of potential metrics since FDA has identified that it is not a discerning metric. Confirmed Laboratory Out of Specification investigations generally are reported as deviations within an organization and can lead to a root cause investigation in the operation.

Conclusion from Comments on Proposed Practice Areas and Metrics

ISPE recommends a collaborative approach to achieve a meaningful comprehensive program for appropriate metrics.

3. Frequency of reporting

There was very strong support from ISPE's survey for establishments to report annually with flexibility for amount of segregation of data based upon current establishment practices. (Annual, Quarterly, Monthly)

4. Additional Considerations

There was very strong support from ISPE's survey for transparency of a voluntary quality metrics program. Establishments wish to receive the final output as well as method of calculation for their data provided to FDA and correlations to proposed FDA goals of the program.

ISPE recommends exclusion of Quality Culture as a quantitative measure. Quality Culture is important to industry and is assessed uniquely within each company. It is recommended that Quality Culture be a consideration within voluntary quality management maturity programs for industry.

ISPE would welcome a better understanding of FDA's change management plan for the Quality Metrics Program including any anticipated piloting and collaboration with industry. Additionally, further clarity is needed with regard to how industry will communicate to FDA changes to submitted data.

ISPE would like to highlight some considerations and areas of caution that could impede the value and benefits that the QM program is striving to achieve:

- Context is an important consideration for effective performance measurement and action taking. Lack of context/analysis details may impede an establishment's ability to identify effective actions to drive continual improvement.
- Releasing data/information to the public too early in the implementation of the QM program could have unintended or negative consequences. Data or information could be misrepresented or misinterpreted, which could result in undue harm to an organization or the public, as well as a breakdown of trust with the public. We request a cautious approach early in the program that allows the Agency and industry to better understand the outputs, prior to sharing information with the public that could be misleading.
- Metrics Drive Behavior: output from a quality metrics program can lead to behavior that can potentially be counterproductive to the industry and agency's aligned goals. Improvements/changes can have an initial impact on metric performance, which can sometimes be construed negatively. We want to encourage changes to be made that strengthen long term value/benefit for the patients, FDA, and industry without fear of short-term impact on immediate metric performance.
- The Quality Metrics Program could prompt firms to focus on the specific, required FDA metrics in the proposed practice areas for their site, driving behaviors specific to improve the reportable metrics. This may have the unintended consequence of reduced focus, or lack of improvement, for metrics outside of the expected practice areas. We believe that the broader view of continual improvement through APQ or QMM will result in holistic Pharmaceutical Quality System improvement as it will include quality system effectiveness, metrics, and continual improvement tools in a comprehensive model.

These considerations would support that any quality metrics program should have a phased implementation to allow learning and for evaluation of potential unintended consequences.

Conclusion

ISPE remains ready to partner with FDA and industry to co-create a meaningful and beneficial quality metrics program.

Appendix 1: ISPE Advancing Pharmaceutical Quality (APQ) Program

ISPE is aligned with FDA's vision of the value of QMM and initiated the [ISPE Advancing Pharmaceutical Quality \(APQ\)](#) program in 2018 as an industry-led approach to advance pharmaceutical quality. The basic framework of the program is to “assess, aspire, act and advance” quality maturity and was outlined in ISPE's comments on the 2018 [Studying Quality Metrics and Quality Culture: Quality Metrics Feedback Program](#) and [Quality Metrics Site Visit Program](#).

The APQ program, which is scheduled to be completed in 2022, provides a framework for assessing and enhancing the effectiveness of the Pharmaceutical Quality System (PQS). The program consists of four Good Practice Guides, one for each of the four elements of an ICH Q10 Pharmaceutical Quality System bookended by an optional benchmarking tool developed by University of St. Gallen. Three guides have been published and are available to use: [Corrective Action and Preventive Action](#), [Change Management System](#), and [Management Responsibilities and Management Review](#). The fourth guide, Process Performance and Product Quality Monitoring System, is scheduled to be published in 2022. The 2017 [ISPE Cultural Excellence Report](#) will be converted into a fifth APQ Guide with enhanced features and case studies and also is scheduled to be published in 2022

The APQ program:

- Recognizes that the ability to advance quality management maturity lies within the industry itself (developed by industry representatives for use by industry)
- Is built upon the ICH Q10 model and enhances the PQS elements with the aspects of cultural excellence, operational excellence (OPEX) and continual improvement
- Provides a comprehensive approach for assessing and improving an organization's quality management maturity to advance the state of quality within the organization

The APQ program focuses on eight overarching goals:

1. Integrate quality management maturity, cultural, and operational excellence principles, tools, and approaches
2. Support and incentivize continual improvement
3. Foster industry ownership of quality beyond compliance
4. Promote effective and efficient use of resources
5. Encourage self-improvement and supplier improvement
6. Enable structured benchmarking, knowledge sharing, and learning among organizations
7. Increase the reliability of supply for quality products
8. Offer routes to delivering sustainable competitive advantage

At the core of the APQ Program is the Assess, Aspire, Act and Advance framework which provides a set of tools, resources, and systematic approaches for organizations to advance the maturity and effectiveness of their PQS.

FDA indicated in the [2022 OPQ White Paper](#) that there must be clear incentives to achieve higher QMM and mentions the incentives could include reduced inspection frequency, increased regulatory flexibility in making post approval changes and improved supply chain insight. FDA Center for Devices and Radiological Health (CDRH) has already offered such incentives in its draft guidance, [Fostering Medical Device Improvement: FDA Activities and Engagement with the Voluntary Improvement Program](#) subject to participants complying with requirements in the draft guidance.

ISPE recommends a voluntary, industry led program for QMM whereby industry can assess, aspire, act, and advance their level of quality management maturity and share it independently with their patients, consumers, customers, and health authorities globally, based upon international ICH Q10 standards. Any QMM program should entail assessment, measures, improvement tools for advancement, and case studies for robust application. Such a QMM program supports Janet Woodcock's oft-quoted vision of Pharmaceutical Quality for the 21st Century.