Executive Summary

ISPE would like to express its appreciation to the FDA for acknowledging receipt of comments made by ISPE in response to the 2016 draft Quality Metrics guidance and welcomes the Feedback and Site Visit programs announced in the June 2018 Federal Register Notices. ISPE is especially pleased that comments relating to engagement with industry, for example real time communication are a feature of these programs, particularly the Site Visit program.

ISPE continues its objective data-driven mission to interact with and provide feedback to FDA on Quality Metrics and related regulatory programs by:

- Gathering and collating technical and operational feedback on the implementation of Quality Metrics to facilitate and progress industry and FDA dialogue
- Continuing to collaborate with St Gallen University, and advancing collaboration with PDA relating to develop of assessment and improvement tools relating to quality culture
- Exploring the value and incentives of adopting a self-assessment program to promote quality maturity understanding and improvement with industry stakeholders based on the ICH Q10 Pharmaceutical Quality System Model and reflecting principles of operational and cultural excellence

These efforts may be useful for future versions of a quality metrics program and provide tools and concepts for inclusion in the evolving New Inspection Protocol Project (NIPP).

Overview

ISPE is grateful to FDA for taking into consideration ISPE's comments made in responses to the 2016 draft Guidance, Submission of Quality Metrics Data [1], the associated Federal Register Notice (FRN) [2], and webinar [3] and that these have been recognized in 2018 FDA Federal Register Notices, Modernizing Pharmaceutical Quality Systems; Studying Quality Metrics and Quality Culture; Quality Metrics Feedback Program [4] and Quality Metrics Site Visit Program for Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research Staff; Information Available to Industry [5]. FDA acknowledges in both FRNs that it is responding to feedback from stakeholders by introducing these two programs:

1. Quality Metrics Feedback Program
2. Quality Metrics Site Visit Program

FDA noted "…it should perform further studies of the FDA Quality Metrics program through a pilot program and additional discussions with stakeholders."

Several substantial elements of these programs are described in the ISPE responses to the 2016 FDA draft guidance [6,7]:

- Engage closely with industry experts to understand which and how quality metrics are used in practice
- Use pilot programs to test concepts
- Use voluntary and phased approaches to adopt quality metrics
- Start small, learn and evolve
- Identify incentives for participation

ISPE Actions to Achieve FDA and Industry Common Goals

As stated in the Quality Metrics Feedback Program FRN, FDA developed a 21st century vision for manufacturing and quality with input from academia and industry. The desired state was described as follows: "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."

ISPE is fully aligned with this vision and is exploring with its stakeholders and membership the interest for an industry-led "Advancing Pharmaceutical Quality" program. At a September 2017 workshop for participants in Wave 1 and 2 of ISPE's metrics program and at which we had the honor of having the presence of FDA representatives, preliminary proposals were developed on potential processes for achieving FDA goals. The themes that emerged included:

- Voluntary
- Phased
- Well-defined assessment criteria
- Incentives/recognition inclusion

ISPE believes that a voluntary program would self-propagate through engagement of early adopters/change ambassadors and would demonstrate industry leadership and commitment to gathering useful experience.

Processes for developing an alternative program should be based on the ICH Q10, Pharmaceutical Quality System Model and could leverage existing programs such as OSHA's Voluntary Protection Program (VPP) and the FDA's Case for Quality Program, which is administered by the agency's Center for Devices and Radiological Health. It could also borrow elements from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) pre-inspection information request process.

The industry-led "Advancing Pharmaceutical Quality" proposed program would:

- Evolve the primary focus from submission of harmonized metrics to establishing a platform for advancing the state of pharmaceutical quality that could be leveraged by industry and potentially FDA to achieve quality metrics program objectives. For example, since the design of the proposed program is based on the ICH Q10 Model, it may assist with providing tools and concepts for the New Inspection Protocol Project (NIPP)

- Integrate culture, quality, and operational excellence tools and experiences, and demonstrate value and continuity to industry, regulators, and patients
- Include assessment and continual improvement tools, education (conference, articles), industry engagement workshops, benchmarking forums, and interactions with regulators, especially FDA

Program goals for "Advancing Pharmaceutical Quality" may include but are not limited to the following:

- Enable and foster industry ownership of quality beyond compliance
- Integrate quality, cultural, and operational excellence principles and learnings
- Support and incentivize continual improvement
- Promote efficient use of resources by improving execution
- Increase reliability of supply for quality product
- Fuel benchmarking, sharing, and learning among companies
- Provide a program that has value to industry worldwide whether it is adopted by regulators or not
- Encourage self-improvement and supplier improvement
- Have potential competitive advantage
- Have potential for the program to be adopted by regulators, providing additional benefits to industry through regulatory interaction and regulatory relief
- Foster the principle of collaboration such that
  - Adjustments and improvements to the program are facile
  - Outcomes and changes are transparent to all involved

Guiding principles for this ISPE initiative include:

- Promoted as "by industry, for industry" at least at the outset
- Must have meaningful and tangible value and benefits to industry
- Recognized as beneficial for regulatory authorities because it is fundamentally based on the ICH Q10, Pharmaceutical Quality System Model
- Applicable across all sectors of the pharmaceutical industry
- Employ "as-is" company data and site procedures as much as possible
- Obviate non-value added and irrelevant approaches and criteria for demonstrating quality metrics and maturity
- Leverage existing methodologies and principles where relevant (e.g. ISO, VPP, MHRA)
- Engage FDA and other organizations in developing models
- Complement existing FDA initiatives (e.g. Quality Metrics, New Inspection Protocol project, data analytics)
- Be simple

These principles were tested at an ISPE workshop of industry representatives in March 2018 and supported. A detailed framework (see section below) was developed for further assessment at a June 2018 workshop with increased industry participation. There was positive interest to progress a limited pilot study

based on evaluation of a site or facility's level of Corrective Actions and Preventive Actions (CAPA) maturity and elements of Management Responsibilities. Results of this pilot will be published and discussed at a session at the ISPE Annual Meeting in Philadelphia on Wednesday, November 7.

Proposed Advancing Pharmaceutical Quality Framework

An overview of the proposed program framework is given in Figure 1.

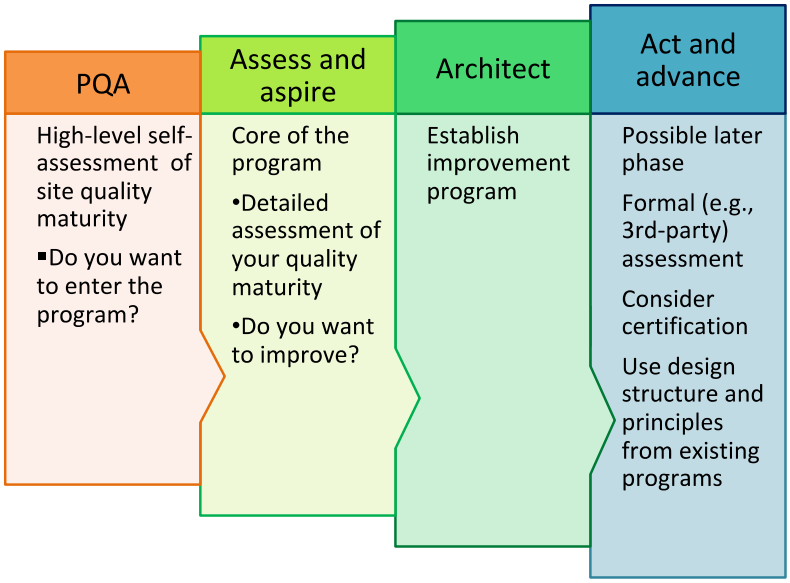

Figure 1: Overview of ISPE Advancing Pharmaceutical Quality Proposed Framework

The core of the program is shown in the middle two columns, where there are two components. The first component would be for an organization to "assess" the company and its facilities' quality maturity against pre-agreed criteria, and the potential for improvement. Should the company choose to proceed and "aspire" to improve, the program would have a framework of tools and key performance indicators (KPIs) that would be the "architect" of that improvement.

As a first step, in the left-hand column ISPE is considering a Preliminary Quality Appraisal (PQA) where the objective is to evaluate if a potential participant is justified in spending more resources to understand their current state of quality, and to assess potential effort and benefit of aspiring to a higher maturity level.

In the right-hand column, there is the opportunity to introduce a more formal assessment of quality maturity, potentially at a later stage, using a third party. This could be recognition of performance using an objective certification system.

A key element of both the PQA and the more detailed assessment would be an exercise to compute the cost of quality—essentially the cost of poor quality. An ISPE team has been considering how to conduct these assessments and will provide suggestions and case studies.

A fundamental basis of the program is ICH Q10, Pharmaceutical Quality System [8] as characterized in Figure 2 and subsequent explanation.

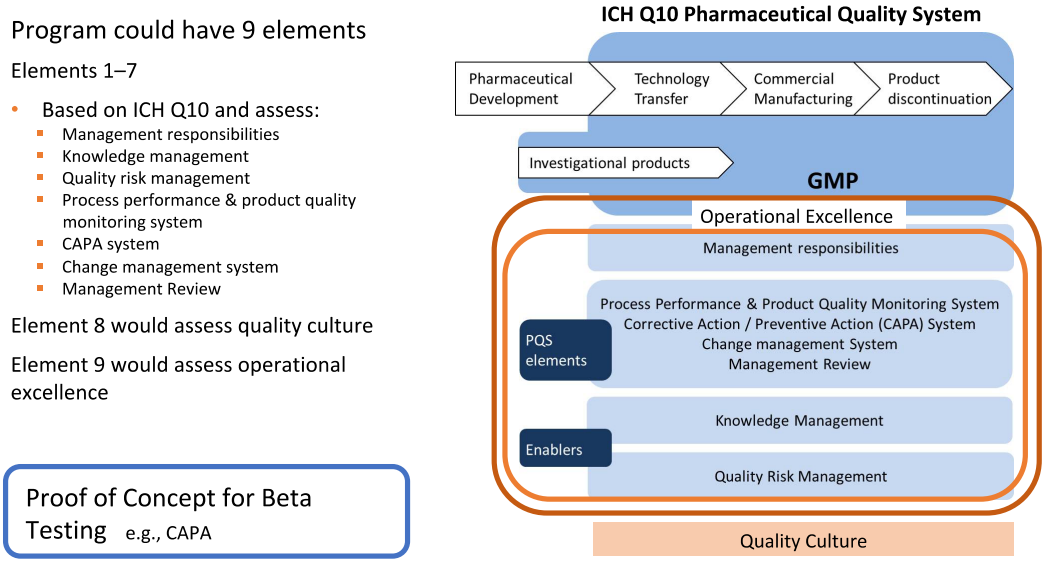

Figure 2: Overview of Relationship to ICH Q10, Pharmaceutical Quality System

To deliver quality product to customers on time and in full (OTIF, a KPI used by many organizations), a site in a supply chain delivering that product should have a quality system that is underpinned by and fits with the site's operational excellence practices. As recommended in the ISPE Good Practice Guide: Operations Management, [9] a company's manufacturing operations policy is likely to be applied differently across a series of sites, due, for example, to different technologies, locations in the supply chain, or geographies, with differences in regulations and staff cultures. Given this, sites may utilize slightly different KPIs to balance operational efficiency and service within an acceptable cost structure.

As demonstrated in ISPE's Quality Metrics Pilot programs, Waves 1 and 2, [10,11] excellence in quality culture is required to deliver robust and sustained quality metrics performance. It is well understood from other studies, such as the University of St. Gallen work with FDA [12], that cultural excellence is positively associated with good business performance. Hence in Figure 2, quality culture underpins all other elements. Tools for assessing and improving cultural excellence are included in the ISPE Cultural Excellence Report. [13] The Parenteral Drug Association (PDA) has also developed and implemented a quality culture assessment tool. ISPE and PDA are engaged in preliminary discussions regarding future potential collaboration in quality culture assessment and improvement.

In ISPE's Pilot Program Wave 2, Corrective Actions and Preventive Actions are an indicator of a company's health, as shown by a relationship between CAPA with preventive actions and total complaints. They demonstrate whether issues are acknowledged, tracked, and, ultimately, remedied in an effective and permanent manner.

The timeliness and robustness of CAPA performance also serve as an indicator of whether a company demonstrates effective planning and/or has sufficient resources to manage and resolve issues that have either occurred or are projected to occur. In this way, the effectiveness of a company's CAPA program is also likely to have a correlation to other key indicators of company health, including, but not limited to, management responsibilities (as defined in ICH Q10). Consequently, CAPA maturity has been selected as one of the Q10 elements to assess early during development of the Advancing Pharmaceutical Quality Framework initiative. Examples of how to evaluate CAPA maturity and how maturity could be improved will be important objectives of the initiative. ISPE is launching a pilot in the fall of 2018 with preliminary results announced at the ISPE Annual Meeting session on November 7.

Part of the vision for this program is for collaboration with regulators during design of the framework of this initiative. Ultimately it is hoped that regulators could adopt and/or evolve relevant parts of the program to help achieve their goals.

Feedback from industry subsectors.

In accordance with FDA's stated intention to continue to engage with trade and professional membership associations to gather feedback from industry subsectors, ISPE will continue to serve as a conduit for providing objective data-driven insights on industry subsector experiences in preparing and executing engagement with FDA as described in these two FRNs.

From a preliminary review and assessment of the two FRNs, companies evaluating participation have provided the following feedback:

- Is there a risk of the FDA having a skewed picture of industry's current practice, if only companies with robust reporting systems participate?
- Will there be a feedback mechanism from the programs and could this in fact be an incentive for engagement? If there is feedback, how will findings be relayed to participants and to the wider industry? How/will they be shared with Office of Regulatory Affairs (ORA) and investigators?
- The incentives for companies to participate in the FRN programs are not self-evident. Additionally, the incentives for what may ultimately be a reportable quality metrics program are also not clear?
- There is substantial effort required to prepare for and participate in the FRN programs and companies will need to balance benefit to burden.
- It is not clear that dialogue will focus on quality metrics programs and not lead to wider investigations into points raised or discussed. Additionally, it is not clear if there would be interest in self-inspection/internal audit programs and how companies will navigate through such requests given how FDA has historically handled these programs.
- FDA appears to continue with a strong focus on product-based metrics while Industry has indicated that that there are limitations and burden associated with product focused metrics. It remains ISPE's position that site-based metrics are more relevant to assess quality standards across the industry.
- The indicated continued interest in "measurement of quality culture" within the auspices of the quality metrics program does give continued cause for concern due to its very nature not being an

objective measurable outcome in itself. Additionally, operational/business performance excellence measures considered to be business vs cGMP indicators and will need context to be meaningful.

- Will information, for example company metric performance, potential or actual continual improvement projects identified by the company provided to FDA be subject to disclosure under the Freedom of Information Act?

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