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ISPE Quality Metrics Project

by Christopher J. Potter on behalf of ISPE's Quality Metrics Project Team

This article describes a groundbreaking ISPE initiative that is responsive to FDA's call to look at metrics that can truly measure quality and compliance as a risk-based way to schedule inspections.

Overview

This article summarizes the rationale, objectives and challenges for ISPE's Quality Metrics project, which is a response by industry to FDA initiatives to help move the pharmaceutical industry toward the "desired state" by defining objective metrics to support a risk-based inspection program. An afternoon session will be held on Monday, 4 November 2013 at the ISPE Annual Meeting to present suggested metrics acceptable to industry in the areas of:

- Out of Specification/Laboratory Failure Investigation Rates
- Batch Failure Rate

Additionally, preliminary ideas will be presented for possible metrics associated with leading metrics and new ideas; some potentially based on the "6 systems"[1] the FDA uses when preparing for an inspection.

The session at the upcoming ISPE Annual Meeting follows a successful workshop held at the FDA/ISPE co-sponsored CGMP Conference in Baltimore, MD, USA in June 2013. During the workshop, a group of dedicated volunteers collaborated with delegates and the FDA to engage in a lively discussion that provided ideas on the overall metrics topic. This group has been endorsed by ISPE's International Leadership Forum and has formed under ISPE's successful Product Quality Lifecycle Implementation (PQLI) initiative. PQLI has been working since 2006 providing workshops, training and industry guides relating to overall quality initiatives sparked by ICH Guidelines Q8, Q9, Q10 and Q11. Major initiatives have emerged from regulators and industry modernizing development, technology transfer and manufacturing, as well as improving quality systems applicable over the product lifecycle.

Background

FDA's vision for 21st century manufacturing in the pharmaceutical industry is often quoted as the "desired state" and is:

> *"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"*

There have been many guidelines issued by the FDA[1,2,3,4] and by the International Conference on Harmonisation (ICH Q8,[5] Q9,[6] Q10[7] and Q11[8]), which have provided a regulatory framework to allow industry and regulators to move toward the "desired state."

Nevertheless, the FDA identified in a Report in 2011[9] that:

> *".....drug shortages have been increasing in frequency and severity in recent years and adversely affecting patient care. Some recent shortages have involved drugs for life-threatening conditions and, in some cases, the product in shortage has been the only product for the patient's condition. While most drugs do not experience shortages, this is a significant public health problem, one that deserves the concerted attention of government and industry."*

The report concluded that:

> *".....the problem of medical product shortages is complex and stems from economic, legal, regulatory, policy, and clinical decisions that are deeply interconnected."*

To assist the FDA and industry to reach the vision, ensure product quality in an ever increasing global supply chain, and to help reduce drug shortages, the Food and Drug Administration Safety and Innovation Act (FDASIA)10 provided the FDA with new authorities. Important provisions relate to enhancing the safety of the drug supply chain. This resulted in new legislative mandates affecting cGMPs in the ever increasing global environment FDA operates in. Gone is the old legislative mandate requiring a two years inspection frequency of all pharmaceutical manufacturing sites and in its place, FDA must now implement a risk-based inspection program. Having and understanding what quality metrics can influence and the legislative provisions newly enacted give FDA the ability to gain information to support such risk-based inspection programs.

Of relevance to this article are Sections 704, 705 and 706 of FDASIA relating to advanced provision of information (e.g., quality metrics) and risk-based inspection programs.

Section 704 *"…enables personnel of the Food and Drug Administration to search the database by any field of information submitted in a registration…"*

Section 705 requires *"risk-based schedule for drugs"* and lists *"risk factors"* as:

(A) The compliance history of the establishment.
(B) The record, history, and nature of recalls linked to the establishment.
(C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment.
(D) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years.
(E) Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809.
(F) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources.

In addition, Section 706 requires *"… records or other information…. be provided….in advance or in lieu of an inspection…"*

FDASIA required formation of a task group to develop and implement a strategic plan for enhancing the FDA's response to preventing and mitigating drug shortages, which has duly been established as the FDA Drug Shortages Task Force (Task Force).

In 2013, an ISPE Task Team conducted and published[11] a Drugs Shortages Survey of the pharmaceutical industry and also concluded:

> *"The study confirmed that drug shortages are multifactorial, often resulting from issues within the quality systems, which can be affected by key aspects of organizational governance and the quality of interactions with regulatory authorities."*

Based for example on FDA information[12] that quality problems (e.g., contamination, presence of foreign particles) are the most common cause of drug shortages, accounting for nearly 46% of all drug shortages in 2011 and other supporting information, and given ISPE's technical expertise, ISPE proposed to focus any further activity on manufacturing and quality issues. The Survey report identified metrics to detect and address shortages as a potential improvement opportunity and states:

> *"Strategies for identifying and implementing appropriate quality and/or other alerting metrics within organizations may prove to be a very important aspect of preventing or mitigating future drug shortages."*

In the Federal Register Notices,[13] the FDA requested public comments on issues related to development of their strategic plan. Public comment was sought on a number of questions, one of which was to assist the FDA in their evaluation of product manufacturing quality. The FDA is exploring the broader use of manufacturing quality metrics and requested input on the following questions:

- What metrics do manufacturers currently use to monitor production quality?
- To what extent do purchasers and prescribers use information about manufacturing quality when deciding how to purchase or utilize products?
- What kinds of manufacturing quality metrics might be valuable for purchasers and prescribers when determining which manufacturers to purchase from or which manufacturers' products to prescribe?
- What kinds of manufacturing quality metrics might be valuable for manufacturers when choosing a contract manufacturer?
- How frequently would such metrics need to be updated to be meaningful?

Metrics data provided to the FDA should be kept confidential to the Agency and the company.

Partially as a response to the request in the Federal Register Notices,[13] partially resulting from the ISPE Drug Shortages Survey, and partially to propose metrics which can assist companies and regulators move toward the "desired state," ISPE has established a Quality Metrics project with the following goal:

- To produce a "white paper" acceptable to industry on quality metrics, which could be reportable to the FDA to support a risk-based inspection program included in Sections 704 to 706 of US Food and Drug Administration Safety and Innovation Act (FDASIA). The "white paper" should be written for publication on the ISPE web site and the proposals targeted for discussion with the FDA and potentially with other agencies.

The white paper should justify why certain metrics are proposed, and others considered and rejected, and justify the choice of site and/or product-based metrics. It also may comment on the relevance of and/or relationship to data already provided to regulatory agencies, e.g., Field Alert Reports.

This article summarizes the concept and rationale for quality metrics, and summarizes the status, challenges and next steps for ISPE's Quality Metrics project.

Concept and Rationale for Quality Metrics

Quality management is a large and difficult subject with much being written by academics and industry quality leaders and with several programs available, such as the International Standards Organization (ISO) 9000 and Six Sigma program developed by Motorola, Inc. in the 1980s. However, Juran[14] and Deming[15] are considered leaders in the field of quality management.

Juran's lectures to Japanese industrial executives in 1954 are considered one of the most significant contributions to modern quality management. With regard specifically to quality metrics, the following points are relevant and taken from the original notes for the lectures to Japanese senior company executives.16 Juran gave five primary areas for executive responsibility, two of which are:

1. *Responsibility for setting up the measurement of what is actually taking place with respect to quality*
2. *Responsibility for reviewing results against goals and for taking action on significant variations*

In the 1954 lectures, Juran suggested a set of "essential" measures of quality including:

- *Share of market*
- *Complaint rates*
- *Costs of customer adjustments*
- *Direct outgoing (physical) quality characteristics and defect rates*
- *Costs of quality*
- *Scrap, rework, and so on*
- *Overhead and hidden factory costs*
- *Delays and upsets*
- *Lost goodwill*
- *Reduced morale*

In summary, development, review and taking action resulting from quality metrics are two of the five important activities of company senior leadership.

ISPE's Quality Metrics Project

Under the sponsorship of senior quality leaders from a range of innovator and generic companies, ISPE's Quality Metrics Project started with a well-attended two hour session at ISPE's CGMP Conference in Baltimore on 12 June 2013 under the joint leadership of Cynthia Salamon, Vice President Global Quality Services, Bristol-Myers Squibb and Russ Wesdyk, Scientific Coordinator, Office of Strategic Programs, who is a member of the FDA's Drug Shortages Task Force. The objective was for ISPE's project team to analyze and use the output from the discussion at this meeting as input to the "white paper" for discussion with the FDA. Since this initiative is very likely to extend to other regions, for example, the European Medicines Agency (EMA) has issued a reflection paper[17] on drug shortages; industry must consider that other regions also may request quality metrics information.

At the June Baltimore workshop, Russ Wesdyk presented the FDA's preliminary thoughts relating to quality metrics, explaining the relationship of quality metrics to:

- FDAs Vision for 21st century manufacturing
- Relevant sections of FDASIA

As discussed in the Background section above, FDASIA allows FDA to collect information that would be available on inspection "in advance or in lieu of an inspection" and requires the FDA to do risk-based inspections. Quality metrics are considered potentially the sort of information that could be provided "in advance."

He defined a quality metric as:

- An objective measure relevant to the quality of a product, site, or system

Ideal metric criteria from an FDA perspective were described as:

- Meet regulations FDASIA sections 706 and 704
- Be relevant
- Avoid unintended consequences
- Be objective and quantitative
- Be applicable across sectors of the industry
- Not be excessively intrusive to industry and easily operationalized by the FDA
- Be understandable

Three examples of potential metrics were presented for feedback:

1. Batch Failure Rate
2. Right First Time
3. Out of Specification (OOS)/Laboratory Failure Investigation Rates

The implications of providing quality metrics are that there could be a path to identifying lower risk products, processes and sites. Additionally, there is the possibility of a pathway toward regulatory flexibility in the form of lower reporting requirements, for example, prior approval supplement to annual report. There could be an ability to differentiate a high quality site needing less frequent inspection, and a pathway to more objective inspections.

Key points for quality metrics are:

- Keep it simple
- Improve objectivity
- Potential for regulatory flexibility
- Build consensus
- Promote the right behaviors (design metrics carefully to avoid unintended consequences)

He explained that the FDA is seeking broad input, listening to industry, for example, via meetings such as the one in Baltimore, reading responses to the Federal Register Notices13 and seeking opinions of the FDA staff. It is felt that quality metrics can be useful for surveillance using both leading and lagging indicators. Two sets of quality metrics are being considered:

1. Risk rank sites and products
2. Better structure inspections

During the Baltimore Workshop, three breakout groups produced responses to the following questions in relation to the three potential metrics highlighted above:

a. Do you measure? How often?
b. How do you define this metric? What are the challenges?
c. What is the benefit to measure this?
d. Suitable for quality metric reporting? If not, what do you recommend?

A fourth group examined possible opportunities to develop potential leading metrics based on new ideas, for example, building on the proposals by Juran, and/or building on the ”6 systems“[1] which the FDA uses in their inspection preparation, including:

1. Quality
2. Production
3. Facilities and equipment
4. Laboratory control
5. Materials
6. Packaging and labeling

Participants in this group were asked to comment on the following definitions:

Leading indicator: an indicator which may be predictive of future performance.

Lagging indicator: an indicator which identifies or signifies past up-to-present performance.

Questions to this group were slightly different and included the following:

a. Do you agree these are definitions of leading and lagging?
b. What are examples of leading metrics that you might use?
c. What is the benefit to measure this?

Early feedback indicated that these definitions were acceptable to this group.

Issues and Challenges

The discussion did indicate that nearly all companies are measuring some metric in relation to quality, for example, almost 95% of companies reported that they track rejected batches in some way and most companies said they tracked OOS. In contrast, only about 65% of companies in that session reported that they had some measure of “right first time.”

However, the challenges are extensive and some are summarized under the following headings:

- How to achieve consistency of metrics (e.g., definition of failure) within companies, between companies in the same sector and between different companies in different sectors (e.g., oral dosage forms, different types of parenteral dosage forms, biologics, drug substance etc.) and different types of process and technologies(e.g., manual vs automated)?
- Does the metric truly reflect quality and/or compliance?
- Are metrics by site, product or company?
- Will quality metrics lead to unforeseen outcomes?
- Will introduction of metrics lead to unacceptable behaviour, either by industry or regulators?
- How to clarify and advance comments made by industry at the Baltimore meeting?

From a review of the feedback from the Baltimore Workshop, the ISPE project team has decided to work in the following three areas:

- Out of Specification/Laboratory Failure Investigation Rates

- Batch Failure Rate
- Leading metrics/new ideas (including six Quality Systems)

There was an insufficient number of companies reporting that they collected "right first time" data, and there was a high number of issues and questions raised by the group; therefore, this topic has been allocated a lower priority.

Conclusions

The ISPE Quality Metrics Team has collated all the input from the Baltimore Workshop, prioritized the work into three sub-projects, and the team is working to produce suggestions for testing first with senior industry leadership, then for discussion with the FDA. Sub-teams are being populated with individuals who expressed an interest in Baltimore in working on this project.

Presentations of suggestions, ideas and status will be given at the ISPE Annual Meeting on Monday, 4 November 2013 in Washington, DC. A "white paper" will be developed subsequently for publication on the ISPE web site, the material from which will be available for discussion with the FDA and maybe other agencies.

There are many issues and challenges to develop quality metrics which are acceptable to both industry and regulators. Nonetheless, there is enthusiasm to move forward and explore what practical and acceptable quality metrics could be developed which are useful to industry and regulators, providing possible benefits to both parties and ultimately the patients.

Quality Metrics Team

Cynthia Salamon, (Team Leader), Bristol Myers Squibb
Ferdinando Aspesi, Novartis
Michael Davidson, Pfizer
Joseph Famulare, Genentech/Roche
Diane Hagerty, Genentech/Roche
Lorraine McClain, Teva Pharmaceuticals
Lorraine Thompson, Novartis

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