



20 December, 2013

## **ISPE Proposals for FDA Quality Metrics Program - Whitepaper**

### **Summary**

This 'white paper' proposes an initial list of quality metrics which are reportable to FDA to support a risk-based inspection program as given in sections 704 to 706 of US Food and Drug Administration Safety and Innovation Act (FDASIA) and assist industry moving towards the 'desired state'. This initial list of quality metrics is considered appropriate as a starting point to the ISPE team, which consists of representatives from a variety of pharmaceutical companies. Suggestions of potential definitions for the proposed metrics are given.

It is recognized that ISPE's quality metrics proposals are mostly site-based, in line with the requirements of sections 704, 705 and 706 of FDASIA. The intention is to start with several indicator metrics and consider refinement in subsequent phases to consider better links to FDA's 'six systems' used in the inspection program and to products.

These proposals are made based on extensive work conducted by ISPE's Product Quality Lifecycle Implementation (PQLI)-sponsored Quality Metrics project team using input from public discussion from two, well-attended ISPE meetings at which FDA representatives were present. Feedback from these discussions and project team work has identified that those companies that collect metrics do so using different business processes and different definitions and with different objectives after review of data. Given this complexity of gathering, analyzing and reviewing data, it is recommended that a pilot program is used to 'kick off' this program.

For this paper, Proposals are given first, followed by the Alternative Metrics Considered, Principles behind the Proposals and Options for Next Steps.

### **Proposals**

The following proposals, other metrics considered and supporting justifications have been generated from an extensive program of work sponsored by ISPE and summarized in Appendix 1. The names and company affiliations of main contributors are given in Appendix 2.

### **Metrics**

Table 1 gives metrics proposed initially for evaluation in a suggested Phase 1 of the program. The relationship is given to FDA's 'six system' inspection elements and to the product. Although not all these proposed metrics are currently gathered in uniform ways to the same definition across all companies consulted, there is consensus that these metrics are practical and meaningful as a starting point.

It is proposed that these metrics are reported to FDA on a site basis with the option for companies to provide an accompanying qualifying narrative if they wish. It should be noted that some of the proposed metrics have product-based elements.

Phase 2 of the program could increase the number of and move to more product-based metrics, for example any of the proposed metrics could be reported on a product-basis, perhaps starting with “Critical” Complaints Rate as a high priority. It should be recognized that product-based reporting is related to approval reference (NDA, ANDA etc.) rather than site, and for some products e.g. OTCs there may not be a similar reference. For companies, it can be very challenging to allocate metrics on a product-basis given the complexity of allocation of a bulk product into multiple pack configurations (stock keeping units (SKUs)), and with potentially one pack configuration destined for multiple markets. Product-based reporting requires further evaluation and alignment before entering even a pilot phase.

**Table 1: Proposed Metrics and Relationship to FDA’s ‘six system’ Elements and Product**

<b>Proposed Metric</b>	<b>Strongest Relationship to a FDA ‘six system’</b>	<b>Relationship to Product</b>	<b>Leading or Lagging Indicator</b>	<b>Rationale and Comments</b>
<b>Batch Rejection Rate</b>	Production, Packaging & Labelling	Strong	Lagging	Already collected by about 95%* of companies in some form. A measure of production quality or packaging and labelling quality.
<b>Rework and Reprocessing Rate</b>	Production	Strong	Lagging	These are not normally reported as a stand-alone quality metric, but may be captured as a financial metric or as part of Annual Product Review. This metric is proposed as a corollary to the Batch Rejection Rate to provide a fuller picture of the production capability.
<b>Confirmed out of Specification (OOS) Rate</b>	Production	Strong	Lagging	Number of OOS is tracked by most companies*. Would expect that batches that are OOS would end up being included in ‘Batch Rejection Rate’ metric. Useful sub-division of Batch Rejection Rate. A measure of production quality.
<b>Unconfirmed OOS Rate</b>	Laboratory	Weak	Lagging	A measure of laboratory performance and potentially has a link to the quality system
<b>“Critical” Complaints</b>	Quality	Strong	Lagging	Strong link to product quality and quality system performance, and

<b>Rate</b>				importantly to the patient. May overlap with Field Alerts or other Health Authority reporting. This metric could be considered amongst the first to be analyzed as product-based.
<b>% Annual Product Quality Reviews Completed on time</b>	Quality	Medium	Lagging	High and consistent values are a leading indicator of a quality system performance. Product-based metric with strong links to quality system performance including resource allocation.

\* From survey at the ISPE FDA cGMP Conference in June 2013

## Scope

It is recommended that data should be provided by site according to the site registration number at a defined frequency (annually is suggested). A site is in scope if it performs any cGMP unit operation for a drug substance or drug product that is included in a drug product sourced to the US. It is suggested that it is optional for a company to submit either:

- Metrics for all products manufactured at that site since metrics are often collected on a site basis
- or
- Metrics for unit operations for those products supplied to the US

It is not recommended that recalls, field alert reports (FARs), biological product deviation reports (BPDRs) and inspection findings are reported to FDA as part of this list since these are already available to FDA.

## Definitions

Table 2 gives proposed draft definitions of metrics. These are a well-considered starting point and further discussion with FDA is recommended.

**Table 2: Proposed Draft Definitions of Metrics**

<b>Proposed Metric</b>	<b>Draft Definition</b> (Values within the defined time period)	<b>Comments</b>
<b>Batch Rejection Rate</b>	<i>Calculation:</i>  Batch Rejection Rate as a percent = number of rejected batches x 100/total number of batches dispositioned during that time period	'Rejected batches' does not include: <ul style="list-style-type: none"> <li>• Batches intended for rework or reprocessing</li> <li>• Partial batch rejections</li> </ul>

	<p><i>Numerator:</i></p> <p>Number of rejected batches = number of batches that are rejected and intended for destruction or experimental use (i.e., no intention to release to the market)</p> <p><i>Denominator:</i></p> <p>Total number of 'batches dispositioned'.</p> <p><i>Definition:</i></p> <p>'Dispositioned' = the final product output from the site that is ultimately intended for commercial use, regardless of manufacturing stage (e.g., intermediate, bulk, finished drug product)</p> <ul style="list-style-type: none"> <li>• Includes validation batches intended for commercial use</li> <li>• Includes only those batches manufactured and/or packaged at the reporting site</li> <li>• In cases where a product (e.g., API) is manufactured for both internal use and external use ('final product output'), count all batches</li> <li>• Includes all batches manufactured and dispositioned into categories such as 'reject', 'hold', 'quarantined' as well as those released</li> </ul> <p>For purposes of this metric, 'batch rejection' refers to a disposition decision indicating that the batch did not meet the requirements of the marketing authorization and any other regulations relevant to the production, control and release of the medical device or medicinal product.</p>	<ul style="list-style-type: none"> <li>• Scrapped batches due to non-quality reasons (e.g., business decisions, expiration dating)</li> <li>• Rejections from in-process monitoring (e.g., rejects from 100% tablet inspection)</li> </ul> <p>'Batches Dispositioned' count does not include:</p> <ul style="list-style-type: none"> <li>• Components &amp; raw materials from suppliers</li> <li>• 3rd party bulk &amp; finished drug products</li> </ul> <p>Batch rejections must be counted by the site where the problem occurred.</p> <p>Each site reports one Batch Rejection Rate value.</p> <p>Reason or root cause will not be reported.</p>
<p><b>Rework and Reprocessing Rate</b></p>	<p><i>Calculation</i></p> <p>Rework and Reprocessing Rate as a percent =</p>	<p>Supplementary to Batch Rejection Rate</p>

	<p>number of reworked and reprocessed batches x 100/total number of batches dispositioned during that time period</p> <p><i>Numerator:</i></p> <p>Number of 'Reworked and Reprocessed Batches' = number of batches that are dispositioned by Quality and intended for rework or reprocessing</p> <ul style="list-style-type: none"> <li>• Includes full batches only (no partial batches, or automatic on-line rejections)</li> <li>• Includes cases where the rework or reprocessing is covered in the marketing authorization</li> </ul> <p><i>Denominator</i></p> <p>Same as for Batch Rejection Rate</p> <p><i>Definition</i></p> <p>For the purpose of this metric rework and reprocessing refers to action taken on a nonconforming product so that it will fulfill the specified requirements before it is released for distribution</p> <ul style="list-style-type: none"> <li>• Reprocessing: action involves repeating the same process steps from a defined stage of production</li> <li>• Reworking: action involves using a process other than that used to produce the original material</li> </ul>	<p>'Reworked and Reprocessed Batches' count does <u>not</u> include:</p> <ul style="list-style-type: none"> <li>• Batches reworked or reprocessed for non-quality reasons (e.g., repack due to change in destination e.g. from UK to Germany)</li> </ul> <p>'Batches Dispositioned' count does <u>not</u> include:</p> <ul style="list-style-type: none"> <li>• Components and raw materials from suppliers</li> <li>• 3<sup>rd</sup> party bulk and finished drug products</li> </ul>
<p><b>Confirmed OOS Rate</b></p>	<p><i>Calculation</i></p> <p>Confirmed OOS rate as a percent = number of Confirmed OOS results x 100/total number of batches tested</p> <p><i>Numerator</i></p>	<p>Does not include in-process control tests that are not filed</p>

	<p>Total number of OOS results</p> <p><i>Denominator</i></p> <p>Total number of batches tested</p> <p><i>Definition</i></p> <p>OOS result:</p> <p>For purposes of this document, the term OOS results includes all test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files (DMFs), official compendia, formulary or applied by the manufacturer when there is not an 'official' monograph.</p> <p>Confirmed OOS:</p> <ul style="list-style-type: none"> <li>• A result after investigation which does not conform to the intended or regulatory specifications</li> </ul>	
<p><b>Unconfirmed OOS Rate</b></p>	<p><i>Calculation</i></p> <p>Unconfirmed OOS Rate as a percent = number of Unconfirmed OOS results x 100/ total number of batches tested in that time period</p> <p><i>Numerator</i></p> <p>Unconfirmed OOS = Total OOS minus Confirmed OOS</p> <p><i>Denominator</i></p> <p>Total number of batches tested</p> <p><i>Definitions</i></p> <p>Unconfirmed OOS:</p> <p>An OOS result which is found after investigation not to be a Confirmed OOS</p>	<p>Includes:</p> <ul style="list-style-type: none"> <li>• All Unconfirmed OOS results for testing conducted at that site e.g. includes testing of raw materials and purified water.</li> <li>• Process Validation batches</li> <li>• PAT results where an 'OOS procedure' has been defined as part of PAT registration approval</li> <li>• Stability Unconfirmed results</li> </ul> <p>Does not include:</p> <ul style="list-style-type: none"> <li>• Environmental monitoring results</li> <li>• Incidents where a sample has not been processed to a test</li> </ul>

		result.
<p><b>“Critical” Complaints Rate</b></p>	<p><i>Calculation</i></p> <p>“Critical” Complaints Rate as a percent =  <math>\text{number of critical complaints} \times 100 / \text{total number of complaints}</math></p> <p><i>Definition</i></p> <p>“Critical” complaint = A critical product quality complaint is one that if confirmed, indicates a failure to meet product specifications, may impact patient safety and could lead to regulatory actions, up to and including product recall. Critical complaints are identified upon intake based on the description provided by the complainant, and include, but may not be limited to:</p> <ul style="list-style-type: none"> <li>i. Information concerning any incident that causes the drug product or its labelling to be mistaken for, or applied to, another article.</li> <li>ii. Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.</li> </ul>	<p>Definition is taken from FDA Field Alert Report requirements. ‘Criticality’ is assigned at point of receipt and values for all assigned “critical” complaints’ are counted within a metric period, whether subsequently confirmed or not.</p>
<p><b>% Annual Product Quality Reviews Completed on time</b></p>	<p><i>Calculation</i></p> <p>% Annual Product Quality Reviews Completed on time = <math>\text{number of Annual Product Quality Reviews completed on time} \times 100 / \text{Total number of Annual Product Quality Reviews}</math></p> <p><i>Definition</i></p> <p>Annual Product Quality Reviews is defined as:  As required by CFR Sec. 211.180, General</p>	

	requirements, section (e) and ICH Q7, GMPs for APIs, section 2.5 or EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Chapter 1, Pharmaceutical Quality System, section 1.10	
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## Data Submission

It is recommended that all sites within scope report annually to FDA by the end of February each calendar year. This would allow time for firms to collect, analyze and understand the data. The report would be against the site registration or location Data Universal Numbering System (DUNS) number.

Industry would provide both the raw data (numerator and denominator) as well as the rate for the proposed metric, so that perspective on the facility may be provided. It is not proposed to submit what products are registered by site, since FDA should already have that information.

## Algorithm

At this stage there has not been sufficient work on a suitable algorithm. Further work is required to understand:

- current FDA experience with algorithms for determining risk-based inspection programs
- how relevant information already provided to FDA such as inspection reports, FARs, BPDRs and recalls could be utilized alongside the proposed metrics

It is desirable for FDA and industry representatives to work in cooperation to develop a suitable algorithm(s).

## Evaluation of metrics

The ISPE Quality Metrics project team has performed some work to collect and compare metrics between companies and found many challenges, mostly relating to:

- Definitions and their interpretation
- Ability to abstract and provide data in consistent and manageable formats
- Ability to analyze data consistently and which allows comparison across sites with different amounts of data from different technologies

It is not recommended that industry or FDA set a numerical target for any metric. The industry is too varied, there are multiple technology types (e.g., devices, biologics, injectables, solid oral), some sites manufacture multiple types of products and conduct several unit operations in a drug product manufacturing supply chain (e.g., API, drug product manufacturing, packaging)

Putting target values on individual quality metrics may drive undesired behaviors



If a certain rejection rate is defined as ‘acceptable,’ sites meeting that target might not have the incentive to look holistically for potential opportunities for quality and compliance improvements.

Further work is recommended to develop facile processes for evaluation of data and feedback mechanisms to companies.

## Alternative Metrics Considered

Significant work has shown that even more work is required to develop consistent, easy-to-collect, meaningful leading indicator metrics, so called ‘advanced’ metrics. Metrics under the following themes are under consideration as presented at the ISPE Annual Meeting and given in Appendix 1.

1. **Quality System Effectiveness**, for example, Corrective Action and Preventive action (CAPA) effectiveness and repeat deviations. In addition to the metrics discussed in Appendix 1, further thought should be given relating to if and how to assess ICH Q10 implementation, for example the business processes of management review and its frequency.
2. **Process Capability** as a series of statistically-based metrics to understand variability. There is considerable discussion of practical possibilities and management processes in Part 4 of ISPE’s guide series, Product Quality Lifecycle Implementation (PQLI<sup>®</sup>) from Concept to Continual Improvement – Process Performance and Product Quality Monitoring System. Cpk has been considered, however, using acceptance criteria given in approved drug product specifications it may be considered a lagging indicator and may provide little further information than Batch Rejection Rate and Confirmed OOS rate. More advanced use of statistical tools using out-of-trend (OOT) limits as a leading indicator requires much further thought since companies set OOT limits internally in a variety of ways with different objectives.  
Potentially some estimates of process capability could be considered in Phase 2 of the program
3. **Quality Culture Index**. These are metrics which are harder to develop into meaningful values as discussed in Appendix 1 but are desirable in terms of their leading proactive approach to quality.

In conclusion, much further work is required to develop into meaningful metrics.

From the work described in Appendix 1, the following metrics were strongly considered:

- Right First Time
- % GMP training on time
- Unplanned Down Time
- On Hold Batch Rate

For all these cases, there was considerable debate regarding definitions, metric data exist in different databases, even within the same company and are difficult to collect, summarize and submit. There was also constant questioning regarding usefulness. Furthermore, some metrics, for example, unjustified long-term product holds would not be tolerated financially, and are generally tracked within Finance/Operations as cost of inventory on hold, again potentially in a separate database.

Relationship to potential drug shortages will be considered by ISPE's Drug Shortages project team in their continuing work and their relevant recommendations will be available to the Quality Metrics team.

## Principles

Metrics must meet the need of supporting a FDA risk-based inspection program and drive acceptable behavior by both industry and regulators.

How provision of metrics is related to inspection frequency and/or scope of inspection should be considered.

Metrics must be acceptable to industry by being:

- Viewed as measures of quality and/or compliance
- Clearly defined to allow consistent reporting across sites
- Objective and meaningful
- Easy to capture
- Easy to report
- Normalized as needed based on factors such as process differences and technical complexity
- Drive acceptable, not unwanted behaviors

Linkage of metrics to the FDA 'Six-system' Inspection Model should be considered.

Consideration should be given to how metrics already provided to FDA such as Field Alert Report (FAR) or Biological Product Deviation Report (BPDR), and information already available to FDA from inspection reports may be used and integrated with proposed new metrics.

Metrics proposed should ideally be a blend of 'lagging' indicators of past up-to-present performance and 'leading' indicators of future performance.

Metrics should not be requested which attempt to catch incomplete or inaccurate reporting. This type of behavior should be picked up during inspections.

## Options for Next Steps

Based on work conducted by ISPE's Quality Metrics project team, it is proposed that a pilot program, potentially with multiple phases, in cooperation with FDA is conducted for a period to be decided with the following goals:

- Examine the practicalities and the process of collecting, analyzing, evaluating and reporting the data, and the feedback loop mechanism to industry
- Further “flush out” any definition discrepancies and understand the challenges of consistency in terminology/language
- “Flush out” unintended consequences
- Provide data and time to allow FDA with industry to develop what a ‘risk-based schedule’ might be taking account of other risk factors as given for example in FDASIA section 705, paragraph 4:
  - (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*
- Help establish a suitable algorithm to produce a risk-based inspection program. Consider how to link with current FDA processes and data provided to FDA (e.g. FARs, BPDRs, Recalls, Annual Reports)
- Consider how the data could be used beneficially by all parties, for example:
  - Allow companies internally to compare their values with their internal performance, and potentially with other companies’ (blinded)
  - Educate industry and FDA
- Provide data and time to consider what ‘regulatory flexibility’ could be considered
- Help decide on next steps for the implementation of this Phase 1 of the program

It is recommended that a 9 month period is considered for the pilot program so that, for example, two sets of quarterly metrics could be gathered with time allowed for evaluation and submission.

## Implementation Options

A pilot study is recommended as discussed above and there are several options suggested below regarding how this could be progressed. There are some principles that the ISPE team strongly recommends for a pilot:

- FDA must be involved
- Industry representatives should be involved in design of the program and evaluation (blinded) of data
- Industry representatives should be involved in design of the algorithm
- A range of sites with different types of operation should be included to evaluate for example, different risk-profiles of a site, types of unit operations, sizes, and location, and product (generic, Rx, small molecule, biotechnology) etc.
- For companies involved, data must be blinded so that a company only has access to its own data, and potentially to high level summary of all data (to be decided)
- There should be a single pilot program, not separate programs run by external organizations

ISPE's 'leading indicator' metrics team desires to continue its important work. Consideration of how this may progress depends on next steps from FDA.

It is recommended that, after FDA has received all proposals from industry, a well-structured feedback mechanism is needed to agree upon next steps. ISPE plans to support such an effort in conferences scheduled for 2014, in smaller forums with industry representative meetings with FDA and is open to collaboration with other industry associations.

### Options for Conducting a Pilot Program

#### 1. FDA runs the Program

There is precedent for this approach with, for example the QbD Pilots for small molecules and subsequently for biotechnology products. FDA can put out a call for participants via a Federal Register announcement. This approach has the advantages that

- FDA staff should be involved deeply,
- FDA should have a higher level of control,
- current processes will be tested and developed with the strength of practical involvement,
- FDA should have a better view of next steps following the pilot.

#### 2. A Third Party Runs the Program

There could be cost implications, however, a reputable partner could be sought that would conduct the program and willingly support the effort. The advantage of this approach is that FDA would have less involvement than Option 1, conserving resources.

Third party partners can be sought from major consulting companies and academia.  
ISPE is prepared to support a pilot program as discussed in this 'white paper'

## **Conclusion**

In conclusion, an initial list of metrics is suggested for evaluation in Phase 1 of a program. Further work is recommended as part of Phase 1 to address challenges of implementation and develop associated algorithm that assist industry move towards the 'desired state'. Phase 2 of the program would consider expansion to include 'advanced' and product-based metrics.

## Appendix 1

### Summary of ISPE Activities

ISPE's Quality Metrics program has consisted of the following activities.

1. 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. 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". Three examples of potential metrics were presented for feedback:
  - a. Batch Failure Rate
  - b. Right First Time
  - c. Out of Specification (OOS) / Laboratory Failure Investigation Rates

Breakout groups produced responses to the following questions in relation to the three potential metrics highlighted above:

- i. Do you measure? How often?
- ii. How do you define this metric? What are the challenges?
- iii. What is the benefit to measure this?
- iv. 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 and the "6 systems" which FDA uses in their inspection preparation.

As a conclusion, 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."

2. The ISPE project team consisting of senior quality metrics professionals from 5 multinational companies has worked in the following three areas using sub teams for each topic to involve senior people from more companies (additional 12):
  - Out of Specification / Laboratory Failure Investigation Rates
  - Batch Failure Rate, changed from Batch Reject Rate since 'failure' is more clearly defined
  - Leading metrics/new ideas (including six Quality Systems)

Proposals were made in each of these 3 areas to an audience of over 250 people at ISPE's Annual Meeting on 4<sup>th</sup> November in the presence of Russ Wesdyk and other members of FDA.

From this meeting, Confirmed OOS Rate, Unconfirmed OOS Rate and Batch Rejection Rate are included in ISPE's list of proposed metrics.

The leading metrics/new ideas sub team considered many potential metrics under the following themes:

- a. Quality System Effectiveness
  - b. Process Capability
  - c. Quality Culture Index
- a. Quality System Effectiveness could be measured by metrics under the following categories:

- i. Corrective Action and Preventive action (CAPA) effectiveness trending
- ii. Deviation trend review e.g. repeat deviations
- iii. Recalls/ Removals/Field Alerts/Reported Events
- iv. Confirmed/Escalated Customer Complaints
- v. Cost of Quality (dollars/dozen or % sales)
- vi. Human Error Deviation %
- vii. Deviations open past "x" days

Much further work is required to assess the utility of these metrics and develop good definitions and for companies to establish consistent tracking systems.

- b. Process Capability is a series of statistically-based metrics to assist with understanding of variability. For example, Cpk could be considered as one statistically-based metric using out of trend limits to help define continual improvement opportunities. Using out of trend (OOT) limits for critical quality attributes (CQAs) could be a leading metric, however, review of industry indicates that few companies routinely measure Cpk, that establishment of OOT limits is not consistent between companies and again there are issues with definitions as well as number of batches to include in Cpk assessment as well as approach to application. Much further work is required to develop practical and meaningful metrics for this one statistical metric. The same experience was found for other statistically-based metrics e.g. PpK, use of control charts
- c. Quality Culture Index should evaluate evidence of investment in resources, time and money in building a company's quality culture. Metrics in this category could be allocated to sub-categories as follows :

- i. People
  1. Technical/QA Training/Education Rate – All employees with direct impact on product/data
  2. Effectiveness of Training/Education
  3. Management Accountability for Cultural development; promoting and supporting quality
- ii. Places
  1. Investment spent in new and existing facilities, equipment, utilities
- iii. Performance
  1. Frequency of Quality Management Performance Review Meetings
  2. Level of proactive actions and assessing trends for signals to drive Continual Improvement projects
- iv. Prevention
  1. Quality Risk Management Processes
  2. Internal Audit Programs
  3. Global CAPAs – Systemic Assessment across networks
  4. Best Practice Sharing to drive continual improvement

At a Breakfast Meeting on 5<sup>th</sup> November, questions were asked of FDA representatives and there were more considered reactions to the initial proposals, which are summarized as:

- FDA is seeking objective measures of product quality, site operations quality, and site systems performance.
  - Both the absolute value and trends of any given metric or suite of metrics might be valuable relative to making both direct comparisons (segmenting products and sites) and promoting continual improvement,
  - Additional metrics can sometimes be useful to provide a fuller picture than a single metric,
  - FDA is seeking input on algorithms for how to use and evaluate the metrics
3. The Project Team has continued work to refine and extend proposals as well as start to investigate what preliminary definitions of proposed metrics could be, and how a proposed pilot could be performed.

This work has led to the proposals given in this ‘white paper’.

Any further work to establish proposed ‘leading indicator’, product-based and ‘six system’ ‘advanced’ metrics should be strongly linked to a pilot program. Output from this ‘advanced’ metrics work should fill gaps in the risk-based algorithm so that better estimates of inspection risk are developed.



## Conclusion

Conclusions from this extensive work are:

- Only about 65% of companies in the June session reported that they had some measure of “right first time.” Based on this information and difficulty with definitions it was decided not to progress this metric as a high priority.
- Many efforts of the team to develop consistent and understandable definitions led to much debate. Suggestions for definitions given in the Proposal are a compromise and not those currently applied by all companies. Change for many companies will be required
- Many of the proposed metrics are not easy for companies currently to collect and provide.
- Definition of a product has been extremely difficult across companies, and sites. For example, for product-based metrics, definition of a ‘product’ is not straight forward - NDA number, pack, stock-keeping unit (SKU)? This complicated issue requires resolution before product-based metrics could be considered further.
- Additionally, metrics are very difficult to allocate to products. For example, drug substance could be incorporated into many drug products, and similarly intermediates manufactured at one site may be sourced into multiple products.
- Sites vary enormously in terms of:
  - number of unit operations performed,
  - where those unit operations sit in the supply chain,
  - size
  - complexity of unit operations
  - risk profile of products – injectables compared with solid oral dosage forms
  - complexity of site

ISPE thanks the volunteers on the various teams for their work to date, support from International Leadership Forum (ILF) sponsors and input from its many members and attendees at its conferences for their valuable feedback. ISPE stands ready through its individual member volunteers to continue to support FDA in its Quality Metrics efforts consistent with ISPE’s strategy of promoting Quality Throughout the Product Lifecycle.

## **Appendix 2**

### **ISPE Main Contributors**

#### **International Leadership Forum Sponsors**

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