24 November, 2015

Division of Dockets Management (HFA-305) *via email*
Food and Drug Administration
5630 Fishers Lane, rm. 1061, Rockville, MD 20852

Re: Docket No. FDA-2014-D-2537

Dear Sir or Madam,

On behalf of the members of the International Society for Pharmaceutical Engineering (ISPE), I am pleased to provide this response to the FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537] and Draft Guidance, Request for Quality Metrics. ISPE appreciates the opportunity to comment on this draft guidance and supports FDA's efforts to implement a quality metrics program. This represents an important initiative by FDA to further implement the vison first established by the cGMP 21st Century Initiative providing for "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight" (Janet Woodcock, M.D. Pharmaceutical Quality Assessment Workshop October 5, 2005).

ISPE would like to highlight the following areas and make certain recommendations to better facilitate this overall goal, and provide industry with the primary responsibility for continual improvement of the processes and products produced. To that end, ISPE:

- Supports FDA's effort to implement a Quality Metrics program
- Supports the need for the program to start with a small, targeted approach
- Recommends a phased introduction
- Is supportive of starting with 3 of the proposed metrics
- Recommends deferring some metrics and data points
- Is concerned that the burden is underestimated
- Requests greater transparency in the manner in which data will be assessed, and outcome and conclusions determined and communicated

ISPE's complete response can be found in the following pages and is based upon data and findings from the ISPE Pilot Program Wave 1, preliminary data and findings from Wave 2, and input from ISPE members and the industry at global conferences and workshops during the past two years.

ISPE is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is

committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators. We stand ready to assist through continued technical and regulatory input to the FDA through the Pilot Program Wave 2, educational conferences, and forums.

If you require additional information, please do not hesitate to contact me or ISPE Senior Vice President for Global Regulatory Affairs, Dora Kourti, PhD.

I look forward to your consideration.

Sincere best regards,

John Bournas
President & CEO, ISPE

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ISPE Response to FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537] and Draft Guidance, Request for Quality Metrics, 27 July 2015

Overview

In response to the FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537] and Draft Guidance, Request for Quality Metrics, 27 July 2015 ISPE:

1. Supports FDA's effort to implement a Quality Metrics program
2. Supports the need for the program to start with a small, targeted approach
3. Recommends a phased introduction
4. Is supportive of starting with 3 of the proposed metrics
5. Recommends deferring some metrics and data points
6. Considers the burden is underestimated
7. Requests greater transparency in the manner in which data will be assessed, and outcome and conclusions determined and communicated

This response contains in Section 1 the Key Messages.

In Section 2, Recommendations and Rationale are given to justify Key Messages.

Comments on the Draft Guidance are given in Section 3.

Comments on and answers to questions in the Federal Register Notice are given in Section 4.

Recommendations, exemplification and justifications are based on data and findings from ISPE Pilot Program Wave 1, preliminary data and findings from Wave 2, and also input from ISPE members.

Section 1: Key Messages

1.1 ISPE **supports FDA's effort to implement a Quality Metrics program** in collaboration with industry to meet the intent of:

- Risk-based inspection scheduling (near term)
- Risk-based principles for reduced post-approval manufacturing change reporting categories (longer term, for example greater than 3 years after introduction of the program)

ISPE considers this a first step toward industry-led programs to facilitate a "maximally efficient, agile, flexible, high quality pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight"

1.2 ISPE supports the need for the program to start with a **small, targeted approach**, to enable both industry and FDA to learn and evolve the program over time. A "Start Small, Learn Evolve" strategy will provide a learning period necessary for implementation of standardized definitions, collection and submission of data within and across industry.

1.3 ISPE recommends a **phased introduction**. There are many approaches that could be adopted, with some possible considerations being:

- Commencing with a phased approach within each of the segments of the industry (finished dosage form, active pharmaceutical ingredient etc.), e.g.,
  - In Final Dosage Forms (FDF), start with higher risk facilities or products (e.g., sterile products and/or medically necessary products with no alternatives)
  - In active pharmaceutical ingredients (API), e.g., exclude specialty APIs or commodities with many product uses)

and

- Voluntary reporting for firms that are not participating during initial learning period with the incentive for firms being the possibility of reduced inspection frequency

1.4 ISPE is supportive of **starting with 3 of the proposed metrics**

- Lot Acceptance Rate (report by site differentiated by product evolving to product differentiated by site)
- Product Quality Complaint Rate (report by product only)
- Invalidated Out-of-Specification (OOS) Rate (report by site)

Additional clarity is requested on definitions. It is very important that definitions are clear and have the most appropriate denominator.

ISPE recognizes the potential value in reporting Lot Acceptance Rate and to a lesser extent Invalidated OOS Rate by product to facilitate review and action as necessary inclusion in a finished dosage form global APR. Currently such a review occurs if there is an identified cause. Given the current maturity level within industry as it relates to aggregating and review of data across the supply chain ISPE recommends that the Quality Metrics program should evolve to reporting at a Product level over time (commence after completion of the initial learning period of 2 – 3 years) and in parallel with the elucidation of the predictive power of the quality metrics program.

Additionally ISPE recommends that facility is provided and used to place quality metric data in context, for example by trending of data.

1.5 ISPE recommends **deferring as potential future metrics or data points**

- Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate
- Optional metrics related to Quality Culture and Process Capability/Performance
- The complementary data point of "lots pending disposition for over 30 days", given the relatively high burden for collection. This data point needs to be further investigated for definition and value of its use

1.6 **Based** on the Pilot program, ISPE is concerned that the **burden is underestimated** in Federal Register Notice (FRN)

- Preliminary data from Wave 2 Pilot program where data was collected for 3 of the proposed metrics indicates that an average of about 25 hours are required to collect data per product in the manner required in the Draft Guidance (cf 10.6 hours in FRN).
- Anticipated costs for firms to establish routine governance processes, adjust internal IT systems and incorporate additional review and retention of data to support verification during inspection should be included in burden estimates
- For many firms reporting by product, differentiated by site presents additional complexity and burden – please refer to Appendix 2

1.7 ISPE requests more clarifications, so that there is **greater transparency on the manner in which data will be assessed/outcome and conclusions determined and communicated**

ISPE recommends that quality metrics data provided to FDA as part of this program are not provided to the public, for example under freedom of information requests. ISPE considers that there should also be an understanding/discussion with stakeholders regarding if and what data could be

shared with other regulatory agencies and the outcome published. ISPE suggests that FDA confirm that there is no possibility of enforcement action related to the Quality Metrics Guidance during the learning period arising from data quality issues while firms establish the quality metrics program within and across sites. Other questions are:

- How data will be used (e.g., public disclosure, freedom of information requests, trending, comments for context, calculation of an aggregate "college board type" score for site, company comparisons or Dean's list)?
- How will this metric component be weighed against the other components in the risk-based approach for inspection scheduling?
- Communication to firms and understanding if their data has resulted in reduced inspection frequency and/or reduced post-approval reporting?

More detail is given below and in the Appendices.

Section 2: Recommendations and Rationale

A summary of the rationale for the Key Messages is given below.

2.1 Implementation of a Quality Metrics program

Recommendation

ISPE **supports FDA's effort to implement a Quality Metrics program** in collaboration with industry to meet the intent of:

- Risk-based inspection scheduling (near term)
- Risk-based principles for reduced post-approval manufacturing change reporting categories (longer term, for example greater than 3 years after introduction of the program)

And as a first step toward industry-led programs to facilitate a "maximally efficient, agile, flexible, high quality pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight"

Rationale

Risk-based inspection scheduling is a stated goal of FDA's quality metrics program as discussed in both the FRN and Draft Guidance. Industry strongly supports advancing towards realization of this goal as it provides benefit to FDA, industry and most importantly patients as resources are directed to ensuring high quality products and resilient supply chains.

Industry supports reduced post-approval manufacturing change reporting categories to facilitate reduction of post-approval submissions, as suggested, for example, in the possibility of "more flexible regulatory approaches'' as discussed in ICH Q8 (R2), Pharmaceutical Development [1] and Q11, Development and Manufacture of Drug Substances [2]. Experience is required, however, perhaps in the form of a pilot study to determine how and on what basis such regulatory flexibility could be achieved. ICH Q8 (R2) does discuss that opportunities for "more flexible regulatory approaches" depend on the quality of an applicant's submission. Hence how a site's quality performance and quality of an application are linked needs to be established.

ISPE has presented a vision of development of an industry led "work space" to further develop metric programs with a potential benefit being achieving transparency of quality performance across industry and leveraging quality as a competitive advantage. It is acknowledged that significant effort is required to further this vision, however, learnings from a phased quality metrics program

could facilitate introduction of such a "work space". Potential opportunities could be:

- Benchmarking: companies understand their quality performance and maturity compared to peers
- Industry Knowledge: In depth statistical analysis, mature process capability, quality culture, targeted research initiatives in the development/maturation of quality metrics
- Collaboration: sharing best practices, engage with regulators at design stage

2.2 Small, Targeted Approach

Recommendation

ISPE supports the need for the program to start with a **small, targeted approach**, to enable both industry and FDA to learn and evolve the program over time. A "Start Small, Learn Evolve" strategy will provide a learning period necessary for implementation of standardized definitions, collection and submission of data within and across industry.

Rationale

The rationale is supported by findings from ISPE Pilot Wave 1 [3] and early feedback from Wave 2, which show the complexity of implementing a standardized quality metrics program.

i. Significant challenges agreeing practical, implementable and meaningful metrics as determined from design and implementation of ISPE Pilots Wave 1 and Wave 2 and from participants in both Pilots, for example:

   - Definitions of 'lot attempted', 'finished dosage form', 'product complaint' and 'specification' etc. require clarification and more detail e.g.

     - For example relating to definition of a lot attempted, different workflow designs result in variety of practices as to when new lot number is assigned. A single lot number could be associated with a single release step or with multiple release steps or no release step. These differences are a function of work order/electronic batch manufacturing instruction design

   More discussion of the complexities, recommendations and questions relating to definitions is given in Appendix 1

ii. Challenges are predicted for firms to submit required data, especially if there is limited support from FDA. In ISPE Pilot Wave 1, a Key Success Factor was the role and substantial effort devoted by McKinsey to assisting participants – see Wave 1 Report sections 5.14, 6.4 and 6.5. For example each site required on average 22 hours of dedicated support to submit using largely current practice site-based metrics. To take the relatively small part of the submission process, firms will be submitting up to about 62 product specific and mandatory data points (from Worksheets for Data Tables in Guidance) per product per site and other information into an as yet untested element of FDA's Electronic Submissions Gateway. Some firms have faced significant resource requirements submitting data to FDA's current ESG for drug listing information – see Section 4, answer to question 4 relating to the Paperwork Reduction Act. ISPE recommends this Gateway process is tested.

iii. The burden is minimized. ISPE is concerned that FDA is underestimating the burden to submit metrics by product then site for firms (average 25.2 hours per product based on a preliminary Wave 2 estimate compared with FDA's estimate 10.6 hours "average burden per response').This is especially the case for firms with multiple manufacturing sites (including potentially external partners as well as internal) and complex supply chains with many products, and for over-the-counter (OTC) compared with Rx and generic (Gx) products – for more detail, please see Section 2.5 below and Appendix 2.

iv. Substantial learning by both parties can be achieved from a carefully designed series of small studies rather than initially involving every pharmaceutical manufacturing site. This approach is analogous to drug development where development studies are almost always performed at a scale smaller than production scale for reasons of cost, availability of materials, time and efficient use of production scale facilities. Manageable amounts of data can be then used to develop algorithms (analogous to a process model) to support a risk-based inspections schedule. Data should also be available to test the correlation between selected quality metrics and the prediction of potential drug shortages.

If benefits from the program for firms are evident e.g., reduced frequency of inspection, the rationale for the program to all firms would be convincing.

A small, targeted approach has clear tangible benefits of allowing complexity to be managed, and the burden on the industry to be reduced as the learning supports more or all firms being introduced later to the program. ISPE recommends that a 3-cycle program (3 years) is allowed to elapse and the program be reviewed before changes are made.

2.3 Phased Introduction

Recommendation

ISPE recommends a **phased introduction**. There are many approaches that could be adopted, with some possible considerations being:

- Commencing with a phased approach within each of the segments of the industry (finished dosage form, active pharmaceutical ingredient etc.), e.g.,
  - In Final Dosage Forms (FDF), start with higher risk facilities or products (e.g., sterile products and/or medically necessary products with no alternatives)
  - In active pharmaceutical ingredients (API), e.g., exclude specialty APIs or commodities with many product uses

And

- Voluntary reporting for firms that are not participating during initial learning period with the incentive for firms being the possibility of reduced inspection frequency

Rationale

A phased approach is consistent with the proposal of a small, targeted approach during which learning can be developed. Many approaches could be considered, for example start with a phased approach within each of the segments of the industry (finished dosage form, active pharmaceutical ingredient etc.). ISPE suggests that FDA develop these in cooperation with stakeholders. ISPE has the following suggestions:

i. In line with a risk-based approach to the program generally, such a risk-based approach could be made to selection of FDF sites. Higher risk facilities are those involved in manufacturing sterile products, especially aseptically filled sterile products as well as other more complex products e.g., modified release products. From a patient perspective, facilities manufacturing medically necessary products without alternatives also pose a higher risk to patients if supply is interrupted. Applying the program to such facilities will also test the hypothesis that quality metrics can assist with prediction of potential drug shortages. Consumer product facilities manufacturing non-dose limiting products (face creams, sunscreen, mouth wash etc.) could be deferred. Adjusting the inspection schedule based on quality metrics data from these facilities even at the reduced scale proposed can itself result in realization of benefits, whether positive (reduced inspection frequency for firms) or negative (poor quality sites identified for FDA) as it targets FDA resources based on

identified risk and furthers the proof of concept of the Quality Metrics program.

ii. API facilities could be selected based on complexity of technology. For example exclude specialty APIs or commodity APIs with many product uses.

ISPE would also encourage voluntary reporting for firms that are not participating during an established phased learning period. A clear incentive for firms to join is the possibility of reduced inspection frequency, which could allow for FDA to redirect inspectional resources to higher risk facilities.

By taking a phased approach:

i. Burden on the industry would be minimized

ii. Benefits could become evident

iii. Flexibility/change agility is maintained. It is anticipated that the identified metrics will most likely need to evolve as the predictive/incisive power of the initial metrics is understood. A phased approach allows for more dynamic evolution of the program, as the industry at large would not be required to establish systems and processes for reporting. Industry burden is consequently minimized and flexibility and agility of the program is maintained as a core element consistent with Dr. Woodcock's vision of "maximally efficient, agile, flexible, high quality pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight"

Additionally, providing for voluntary entry to the program has significant advantages:

- Program would still be relatively small although it may expand as benefits become evident
- Firms volunteering would be looking for benefits and when these are evident the program would have great support and build on these benefits
- The program could generate early benefits for industry and participating firms could be ambassadors for the program.
- A firm could chose to use participation in the program as competitive advantage, for example a CMO
- The burden question would not be relevant since firms 'volunteering' would by design have accepted the required commitment of resources to collect and submit the data as requested.

It is also acknowledged that FDA may request firms with a poor compliance history or under close regulatory scrutiny to participate in the program. Alternatively firms with a poor compliance record would have increased inspection frequency.

2.4 Start with 3 of the Proposed Metrics

Recommendation
ISPE is supportive of **starting with 3 of the proposed metrics**

- Lot Acceptance Rate (report by site differentiated by product evolving to product differentiated by site)
- Product Quality Complaint Rate (report by product only)
- Invalidated Out-of-Specification (OOS) Rate (report by site)

Additional clarity is requested on definitions. It is very important that definitions are clear and have the most appropriate denominator.

ISPE recognizes that the potential value in reporting Lot Acceptance Rate and to a lesser extent Invalidated OOS Rate by product to facilitate review and action as necessary inclusion in a finished dosage form global APR. Currently such a review occurs if there is identified cause. Given the current maturity level within industry as it relates to aggregating and review of data across the supply chain ISPE recommends that the Quality Metrics program should evolve to reporting at a Product level over time (commence after completion of the initial learning period of 2 – 3 years) and in parallel to the elucidation of the predictive power of the quality metrics program.

Additionally ISPE recommends that facility is provided and used to place quality metric data in context, for example by trending of data.

Rationale

ISPE recommended from ISPE Pilot Wave 1 Lot Acceptance Rate and Critical Complaint Rate as 2 metrics in a 'starting set' [3]. The ISPE definition of Critical Complaint rate appears to be a subset of Product Quality Complaint Rate given in the FDA Guidance, both definitions referring to potential specification-related failures.

For Lot Acceptance Rate ISPE's rationale is that Lot Acceptance Rate had in Wave 1 a relationship to Critical Complaint Rate, an important quality outcome. It also had a statistically significant relationship to quality culture scores and to Deviations Recurrence. Given that metrics in Wave 1 were collected on a site-basis, Lot Acceptance Rate is considered to be a strong starting metric to provide an estimate of site performance. Again there are questions regarding changes to the definition - please see more detailed comments in Appendix 1.

Product Quality Complaint Rate is additionally an important quality outcome metric. From the ISPE Pilot Wave 1, this hypothesis was supported by Critical Complaints being statistically significantly related to Deviations Rate and with potential relationships to US Recalls and Lot Acceptance Rate. ISPE supports Product Quality Complaint Rate as a starting metric. ISPE also recommends changes to the definition for finished dosage form to reflect the number of Complaints relative to the number of packs released, not number of lots released as this value is closer to the actual amount sold to the customer, representing an opportunity for complaint. For API facilities the definition should reflect the number of complaints per lot of drug substance. See Appendix 1 for more comments relating to definitions.

Invalidated Out-of-Specification (OOS) Rate is considered by ISPE and many participants in ISPE Pilot Wave 1 as a measure of laboratory performance and ISPE supports its inclusion. This metric did not show relationships in Wave 1 of the ISPE Pilot, however, it is being tested further in Wave 2. In line with ISPE's recommendation for quality metric data to be submitted based on using practices operated currently by most of industry, it is recommended that data are submitted initially on a site basis. Additionally ISPE has recommendations regarding the definition - please see Appendix 1.

ISPE recommends reporting these three metrics with the recommended reporting format:

- Lot Acceptance Rate by site differentiated by product evolving to product differentiated by site
- Product Quality Complaint Rate data by product
- Invalidated OOS Rate by site

for the following reasons:

i. Quality Metrics data are compiled across the pharmaceutical sector currently, however data is most typically compiled and reviewed at a site level. The reporting recommendations given above are more representative of how industry is currently gathering metrics data. Consequently, collecting data in these manners will reduce the burden during start up of the program. This approach will also minimize the potential for data quality issues during collation and aggregation of data across multiple sites to report at a product level.

   The burden to collect Lot Acceptance Rate and Invalidated OOS Rate metric data by product then site in a standardized manner is significant due to additional data aggregation across the supply chain. Key data are:

   - Collecting data by product as requested by FDA and performed in Wave 2 is estimated from preliminary data (Appendix 2) to add

approximately 330% to the burden (3.3 times) compared to collecting by site (1.6 million hours across industry by product compared with 0.37 million by site).

- For complex supply chains one product used 149 hours to collect data by product across 10 sites compared with an average of 11 hours for products manufactured at only 1 site.
- Furthermore, OTC products took approximately 3 times more hours on average (21.1 compared with 7.2) to collect than Rx/Gx products.

Product Quality Complaint Rate data are currently collected mostly at a central level and reporting of these data to a common definition will be a burden, however, this should be minimized by collecting on a central basis.

Please see Appendix 2 for more data.

ii. Consistent with approach of current site-based inspections and promotes ownership and oversight of the metrics at a site level.

iii. Quality problems related to manufacture of a product are often site based, for example with:

i. Process
ii. Facilities
iii. Procedures

This is recognized in FDA's Drug Shortages Strategic Plan [4], a relevant paragraph from section 1B. Root Causes of Drug Shortages being:

> *More often, however, failures in product or facility quality are the primary factor leading to disruptions in manufacturing (Figure 2). In 2012, for example, based on information collected from manufacturers, FDA determined that the majority of production disruptions (66%) resulted from either (1) efforts to address product-specific quality failures (31%, labeled Quality: Manufacturing Issues in Figure 2) or (2) broader efforts to remediate or improve a problematic manufacturing facility (35%, labeled Quality: Remediation Efforts in Figure 2). Quality or manufacturing concerns can involve compromised sterility, such as roof leakage; mold in manufacturing areas; or unsterilized vials or containers to hold the product—issues that could pose extreme safety risks to patients.*

iv. Improves data quality since data generated at a site are submitted without transfer to another establishment when there is additional risk of data quality issues arising from transfer/data transcription errors.

v. Issues arising from Lot Acceptance Rate and particularly Invalidated OOS Rate data are best analyzed and acted upon at a site. These issues could be systematic for a process operated at a site or a site laboratory, not product-based. There is also potential with product reporting to lose visibility of these systematic issues.

vi. Provides important direct input to FDA without the additional burden of aggregating multiple site product data associated with the more complex supply chains. FDA has indicated that with their anticipated robust data collection and analytics that FDA would be able to aggregate data to a product level if required, minimizing the initial burden for much of industry

Collecting and reporting metric data from contract manufacturing organizations (CMOs) will be complex and take time given that data should be verified by the license holder prior to their submission. The requested data is not currently routinely gathered/shared between CMO/license holder and, therefore, mechanisms to verify data back to its source would need to be established (e.g., Invalidated OOS, Total # tests). Data review does not always occur during a current site-based inspection and therefore would be an additional burden for the CMO and the license holder. ISPE recommends however, that data are reported by the CMO after agreement of the data with the license holder.

In summary, this recommended approach to reporting of data could be considered as using practices operated currently by most of industry.

Additional clarity is requested on definitions. In summary, definitions must:

- Be clear. Variability of practices in the industry should be considered and accounted for.
- Have the right denominator (normalization) for metrics calculations. The logic for choosing many proposed denominators is not clear (e.g., Invalidated OOS Rate double normalization, normalization for Complaints Rate with Lots released)
- Allow establishments to report according to the APR/PQR schedule is preferable to minimize burden

There is extensive evidence from ISPE Pilot Wave 1 that definitions must be clear and understood by participants. The following is an extract from section 6.2 of the Wave 1 Report [3]:

Definitions are extremely important:

- *Definitions must be exact: Denominators in particular are highly sensitive to issues around lot aggregation and final disposition.*
- *Even common terms like "lot," "deviations," "complaints" and*

"reviews" must be specified in great detail to minimize multiple interpretations.

- *Even with detailed definitions, support and answering questions throughout the process is necessary to ensure more accurate data submission.*
- *Standardized definitions will differ from current company definitions, thus requiring additional work.*
- *Product and process differences will generate differences and variations in metric ranges.*
- *Commentary on data points is essential to interpretation and analysis*
- *Some variation must be expected due to differences in product, process flows and product/process complexity.*

The pilot showed that standardizing metrics definitions across companies is feasible.

ISPE recommends that additional clarity would be beneficial for definitions of the requested data to ensure consistency in interpretation across industry, such as:

- Invalidated OOS Rate - nonstandard definition appearing to include a double normalization
- "Specification-related rejects" – term "specification" can have very broad interpretation therefore request examples to ensure full understanding of intent
- Finished Dosage Form
- Lot Attempted
- Product Quality Complaints

Further elaboration is given in Appendix 1.

2.5 **Deferring APR/PQR on Time and Optional Metrics as Potential Future Metrics and the "lots pending" data point**

Recommendation

ISPE recommends **deferring as potential future metrics or data points**

- Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate
- Optional metrics related to Quality Culture and Process Capability/Performance
- The complementary data point of "lots pending disposition for over 30 days", given the relatively high burden for collection. This data point needs to be further investigated for definition and value of its use

Rationale

ISPE recommends that FDA-proposed metric of Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate and Optional Metrics are deferred and only considered when the program is established based on the following rationale:

i. Deferring APR/PQR on Time Rate, Optional Metrics and a complementary data point is consistent with the start small, targeted approach

ii. ISPE questions the value of Optional Metrics in the initial phase of metrics collection. The language and purported benefit suggests that a reduced inspection frequency is influenced by the submission of optional metrics. If this is the case, FDA should be transparent, as practically, Optional Metrics would then become mandatory for firms wishing to have the option of a reduced inspection schedule.

iii. ISPE is concerned about the potential unintended consequences that can potentially be driven by the APR/PQR on Time Rate metric. Specifically:

- The APR/PQR metric as defined focuses on time and not other relevant product quality factors, which could result in diminished quality at the expense of achieving the on time performance. .
- Findings from ISPE Pilot Wave 1 indicate that APQR on Time is not a highly differentiated metric. Consequently it is considered that provision of these data would not add value and not assist differentiating quality performance.
- There are questions regarding definitions such as 'what is a drug product' for APR and what is the 'due date' for APR and PQR?

For more detail, please refer to further comments in Appendix 3.

iv. It is broadly accepted that measurement of quality culture is not possible using conventional metrics. Although important, ISPE recommends that assessment of the state of quality culture remains with firms/sites to evaluate in a manner appropriate to that firm/site and is best assessed through on site inspection than through the provision of surrogate metrics that may have limited applicability/relevance across industry.

v. Some high level comments on the proposed Optional Metrics are:

a. Quality Culture:

The question on Senior Management Engagement as proposed is likely to provide answers that are not related to a firm's quality culture. For example "signing' by 'head of a quality unit' not at a site may not lead to any relevant action whereas "signing' at a less

senior site level could lead to the appropriate actions being identified and taken. Signing of the APR(s) is not a true indicator of Senior Management Engagement. Sites and firms vary widely in size and complexity. Senior management should ensure strong product and quality system governance and provide adequate resources to address product, process or facility that may be identified in APR or other management review activities. Signing of an APR does neither guarantee that this is taking place nor suggests that it is not taking place if the signature is not present.

b. CAPA Effectiveness:

    a. In ISPE Wave 1, the definition of CAPA Effectiveness was particularly difficult to achieve.
    b. CAPA effectiveness is best evaluated more broadly by reoccurrence of similar deviation, complaint, OOS and other deficiency. Focusing on retraining as one outcome of a CAPA Effectiveness exercise is a very small element of quality culture and ISPE questions the value of this as a good measure of CAPA effectiveness. The definition of retraining could also be open to very broad interpretation further confounding the relative value of even a narrow focus on CAPA effectiveness.

c. Process Capability:

ISPE's position is that process capability measurements are effective tools for identifying continual improvement opportunities, however, they should not be reportable metrics for the following reasons:

- Choice of process capability tool depends on the situation, there is no one tool that can be applied to all situations
- There are not objective criteria agreed across the industry to judge an incapable process
- Not all CQAs have the same level of risk, nor are amenable to process capability calculations e.g., impurities near limit of detection (LOD)/limit of quantitation (LOQ), microbiological counts, test with multiple stages (dissolution)
- Cpk and Ppk typically cannot be used for all critical quality attributes
- Estimating process variability from a large number of lots gives different confidence intervals compared with a lower number. Many products are not manufactured sufficiently frequently to estimate true mean and standard deviation

well, for example greater than about 25 lots are required to estimate a process capability value.

- Cpk and Ppk values depend on quality attribute acceptance criteria in specifications and these acceptance criteria are established with reviewers based on judgments and limited number of batches. They are inconsistently established between attributes in same specification, between products in the same company and between companies. The concept of process capability as practiced in other industries is not consistent with the current control of variability in Pharmaceuticals.

Given this position 'yes' or 'no' answers to the questions provided by firms electing to submit are unlikely to provide meaningful information given the burden to report these data on a product-by-product basis and for each site. More information should be available on process capability from ISPE Pilot Wave 2 where these questions are asked. FDA if it wished could obtain information on application of process capability measurements during inspections.

vi. "attempted lots pending disposition for over 30 days":

This data point has a high burden of an average value of 0.9 hour per product per site to collect based on preliminary data from Wave 2. This value should be compared with data points of Lots attempted and Total tests performed (both about 1 hour per product per site) and Total company complaints (0.3 hours per product per site) and Invalidated OOS (0.4 hours per product per site). See Appendix 2.

Given that this is not a primary data point and with this high burden, ISPE recommends that this data point is deferred.

Deferring these metrics and data point would allow learning to be developed from 'starting with a small, targeted approach with a phased introduction' and more extensive examination of the utility of these metrics, for example from external research activities. It is recommended that a minimum of 3 cycles (years) of learning and data and should be obtained before considering changing the program.

Further comments on the APR/PQR on Time metric and individual proposed Optional Metrics are given in Appendix 3.

2.6 **Burden**

Recommendation

ISPE recommends **deferring as potential future metrics or data points**

- Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate
- Optional metrics related to Quality Culture and Process Capability/Performance
- The complementary data point of "lots pending disposition for over 30 days", given the relatively high burden for collection. This data point needs to be further investigated for definition and value of its use

Rationale

Please refer to the detail given in Appendix 2. The FDA burden calculation estimate appears low. Wave 2 estimate of the burden to collect 8 data points (cf FDA 15 data points) is 25.2 hours on average compared with FDA's estimate of 10.6 hours "average burden per response". ISPE's estimate is 2.4 times that of the FDA.

To support minimizing the additional burden ISPE has made recommendations, which can be summarized as:

- Start with a **small, targeted approach**
- Use a **phased introduction**
- Start **with 3 of the proposed metrics**
- **Defer as potential future metrics** APR/PQR on Time Rate, proposed Optional Metrics and the data point "attempted lots pending disposition for over 30 days"
- Start **reporting initially using practices operated currently by most of industry**
- Report data annually rather than quarterly (see answers to FRN questions in Section 4)

2.7 **Greater transparency**

Recommendation

ISPE recommends that quality metrics data provided to FDA as part of this program are not provided to the public, for example under freedom of information requests. ISPE encourages FDA to facilitate an understanding/discussion with stakeholders regarding if and what data could be shared with other regulatory agencies and the outcome published. ISPE recommends that FDA confirm that there is no possibility of enforcement action related to the Quality Metrics Guidance during the learning period while firms establish the quality metrics program within and across sites. Other questions are:

- How data will be used (e.g., public disclosure, freedom of information requests, trending, comments for context, calculation of an aggregate "college board type" score for site, company comparisons or Dean's list)?

- How will this metric component be weighed against the other components in the risk-based approach for inspection scheduling?
- Communication to firms and understanding if their data has resulted in reduced inspection frequency and/or reduced post-approval reporting?

Rationale

Industry requests clarity please relating to the above questions since answers impact significantly on how firms interact with, for example:

- FDA and other regulatory agencies
- Customers
- Clients
- General Public
- Other companies

ISPE comments require much of the Draft Guidance and Federal Register Notice to be amended.

Section 3: ISPE Comments on FDA Draft Guidance, Request for Quality Metrics, 27 July 2015

Section	Line Number	Comment	Proposed Change	Rationale and Recommendation
General		ISPE: 1. Supports FDA's effort to implement a Quality Metrics program 2. Supports the need for the program to start with a small, targeted approach 3. Recommends a phased introduction 4. Is supportive of starting with 3 of the proposed metrics 5. Recommends deferring some metrics and data points 6. Considers the burden is underestimated 7. Requests greater transparency on manner in which data will be assessed /outcome and conclusions determined		Please see rationale in Section 2, Recommendations and Rationale
		The text links use of quality metrics data by FDA for risk-based inspection scheduling and prediction of drug shortages (e.g., Section B). ISPE considers the linkage to prediction of drug shortages is not proven.	Propose that text be revised, to either remove reference to drug shortages or provide further information and clarity on how quality metric data selected by FDA will assist with prediction of drug shortages	The link of FDA's proposed metrics to prediction of drug shortages requires establishing – please see Appendix 4.
		Throughout the guidance there is inaccurate use of ICH nomenclature. In most cases 'continuous' should be 'continual' and 'specification' often is applied to acceptance criteria for individual attributes rather than '…a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests	Encourage FDA to use industry adopted and standardized terminology in the final guidance	Meet FDA and international standards Clarity

		described' as given in ICH Q6A and B (e.g., line 727).		
		Has the agency evaluated the inherent, unintended impact of reported metrics whereby manipulation of metrics may occur in order to minimize negative outcomes? For instance, it may be in the best interest of public health for an establishment to be conservative and reject product when quality or compliance is suspect. The impact of the regulation may push that establishment toward more risk. For example, rejecting product, extending investigations to more thoroughly determine and confirm root cause, and testing more than the minimal parameters for the sake of product knowledge are in the public (and the establishments) interest, but will be viewed negatively under this proposal.		
		Will there be a statistics-based threshold of the number of lots manufactured below which reporting is not required? For example 20 lots/year.	Recommend introducing in the scope of the program a number of batches of product below which it is not necessary to submit or below which a considered conclusion is reached by FDA in their analysis	Products manufactured in low numbers of batches could produce values for all metrics that are high e.g., 1 batch failure from 2 batched attempted is 50% rate. Application of this approach could reduce the burden of an initial, small, targeted program.
Opening box	3 to 10	This box seems to allow alternative approaches. If the program is mandatory, ISPE recommends removal of the box. If the program is voluntary, then some relevant text in the box could remain		Mandatory program should not allow alternatives Voluntary approach could allow alternatives
I. Introduction	General for section	The text includes reference to how the data will be used, however, these explanations are not included e.g.	Suggest text Revision	Explanations are not included and should be included either in the Guidance or in supporting explanatory documents

	22-26	'*This guidance includes an explanation of how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to collect data and use quality metrics to help ensure that their policies and practices continue to support continual improvement and innovation in the pharmaceutical manufacturing industry*.' And '*Rather, FDA intends to use quality metrics data in context with other sources of quality data, as further described in this guidance*.'		More detail on proposals with reasons should be given either in the Draft Guidance or FRN
	19, 20	The following text should be changed; 'to improve the Agency's ability to predict, and therefore, possibly mitigate, future drug shortages;'	Recommend revision of the text to "to improve *the firm's* and Agency's ability to identify potential drug shortages and possibly mitigate future drug shortages"	Firms should have the primary responsibility to manage drug shortages assisted as necessary by FDA.
	67	Some foreign establishments are mentioned but these are not understood. '*quality metrics data for certain foreign establishments that are not required to register*'	Encourage inclusion of further explanation required to define what certain foreign establishments are not required to register	There is lack of understanding
II. Background	82 to 169 General for section	See General Comments relating to drug shortages		
	166 to 169	The following text is not clear 'However, if the integrity or utility of the quality data submitted is found questionable based on FDA's evaluation of submitted data or other information, such as an on-site inspection, the uses to which we would put the reported quality data would need to be re-evaluated, along	Rephrasing suggested for enhanced clarity	Intent of the statement is not clear

		with the nature of future requests.'		
	216 to 219	This section (lines 216 to 219) also expands the detail of information which should be reported in 21 CFR 211.180(e)	Recommend that the text be maintained as that in 21 CFR 211.180(e)	FDA is developing new requirements outside of the scope of quality metrics through text in this Draft Guidance.
IV. The Use Of Quality Metrics And Effects Of Non-Reporting	260 to 322 General for section	The section should include a better example of when inspection frequency may be reduced. The section also includes description of what in reality is an experimental program. This lack of certainty in conjunction with ISPE experiences with ISPE Pilot Program, Wave 1 lead to the recommendation that the FDA should start with a **small, targeted approach.**		See detailed comments below
	269 to 272	Inspection frequency being linked to '*highly controlled manufacturing processes'* is not a good example. It is recommended that an example is created linked to quality metrics, the subject of this Draft Guidance.		'*highly controlled'* is a new phrase and not defined. It is also not a quality metric proposed in the Draft Guidance. Hence how can it impact inspection frequency? Quality performance of a site is more than 'control' of processes Sites may have processes with a range of performance and have procedures and capability, which linked with 'good' quality metric and other information may justify a reduced frequency of inspection.
	276 to 284	The second paragraph is describing an experimental process. Answers to these questions should be gained using a Pilot Program leveraging experimental design as appropriate rather than requesting the whole pharmaceutical industry to submit data. The first sentence of this paragraph is difficult to understand.	Please consider focusing the text on how FDA intends to develop a risk-based inspection schedule	Text justifies a Pilot Program
	294 to 311	The fourth paragraph recognizes that single data points may be of limited value, however, the Guidance does	It would be beneficial if The Guidance contain more discussion of	ISPE has been consistent in indicating that 'trending' and/or context of metrics is essential to assist with interpretation of quality metrics data

		not explain how trending will be accomplished	how trending will be developed.	
	296 to 301	The following text should be reconsidered 'For example, the use of new, in-line analytical technology used for real time release testing with increased sensitivity might result in better detection of in-process out of specification (OOS) results and a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will allow for improved assurance of quality. FDA is sensitive to this possibility and continues to support and encourage the use of modern manufacturing technology.'	Encourage inclusion of an example more applicable to use of quality metrics in several industry sectors	The example chosen is very specific and even when PAT is introduced the example could have a low chance of occurring. A quality metrics example should be given such as apparently low Lot Acceptance Rate when a small number of batches are manufactured.
	299 - 300	Delete "diversion in "…diversion and rejection of poor quality product."	…~~diversion and~~ rejection of poor quality product."	Diversion has a variety of implications
V. Reporting of Quality Data and Calculation of Quality Metrics	325 to 643 General for section	ISPE recommends: 1. Start with a **small, targeted approach** 2. Use a **phased introduction** 3. Start **with 3 of the proposed metrics** 4. **Defer as potential future metrics** APR/PQR on Time Rate and proposed Optional Metrics 5. Start **reporting initially using practices operated currently by most of industry** 6. Report data annually rather than quarterly More clarity and detail on definitions are given in Section 2 and Appendix 1		
		How would a site handle a discontinued product from a reporting perspective?	Clarification recommended	
A. Who Reports and Who May Contribut	331 to 403 General for section	ISPE recommends one report for **each site** for finished dosage form (FDF) manufactured at that site. ISPE recommends initially starting with **reporting by site,** (revise	ISPE recommends that Text and templates be revised consistent with the change in reporting format	A suggested revised template is given in Appendix 5

e to the Report		reporting templates) for Lot Acceptance Rate and Invalidated OOS Rate. Product Complaint Rate should be collected and submitted by product. For API data it is recommended that the API site provides these data. ISPE recommends however, that data are reported by the CMO after agreement of the process and/or data with the license holder.		
	374	The phrase 'one report for each API of a covered drug product,' is not clear.	Clarification of requirement is requested	The requirement is not clear. Is it that supplier has to supply one report for every product that that API goes into or one report for their site that includes all API/associated products? As written, API manufacturers may have different interpretations and reach different conclusions. ISPE's recommendation is that provision of API data should be by site and fall under the recommended phased approach suggested in Section 2.
	384	Further clarification of the phrase is requested 'the quality control unit (QCU) in each reporting establishment'	Rephrase is recommended – there may not be a Quality Control Unit in a reporting (corporate) site (e.g., complaints)	If product then site reporting, it is likely that companies would set up or use an existing central corporate function to submit data, which may not be strictly a site 'quality control unit'
	388 to 400	The issue with 'foreign establishments' is not understood	Clarification is recommended	Are 'foreign establishments' not documented in NDAs, BLAs, ANDAs and DMFs?
	398 to 400	In the absence of complete information from 'foreign establishments' it is difficult to understand how FDA can assess the 'state of manufacturing'	Clarification or deletion is suggested	It is difficult to understand how to structure reporting from foreign establishments who are not registered with the FDA and how to manage reporting additional data if FDA requests data for which there is no definition or process in place to collect the data. This could lead to companies being penalized for not providing data from foreign establishments or additional unanticipated data.

B. Quality Metrics that FDA Intends to Calculate	405 to 436	ISPE is supportive of **starting initially with 3 of the proposed metrics** • Lot Acceptance Rate (report by site differentiated by product evolving to product differentiated by site) • Product Quality Complaint Rate (report by product only) • Invalidated OOS Rate (report by site) ISPE recommends that additional clarity would be beneficial for definitions.	Recommend revision of the Text and templates e.g., it should be simplified to metrics proposed for collection and their definitions. Future proposals should be subject to further Guidance	Please refer to Section 2 and Appendices
	434 to 436	ISPE recommends to defer APR on Time Rate as a potential future metric		This recommendation is consistent with the start small targeted approach.
	438 to 448	ISPE recommends **to defer Optional Metrics as potential future metrics**	ISPE recommends clarification and further discussion on the role of Optional Metrics. It is difficult to understand how an algorithm to calculate a risk-based inspection schedule could be based on Optional Metrics	This recommendation is consistent with the start small targeted approach See further comments in Appendix 3
	450 to 483	Optional Metrics, Quality Culture	Further comments are given in Appendix 3	
	484 to 515	Optional Metrics, Process Capability/Performance	Further comments are given in Appendix 3	
	502 to 503	The sentence 'Specifications must be meaningful in terms of achieving the desired finished product characteristics.' should be deleted	Recommend Deletion	Specification acceptance criteria are agreed with reviewers at time of approval or given in monographs. Discussion of this process is not relevant to this Guidance.
C. What Quality Data Would Be Reported	517 to 570 General Comments on section	Data points related to APR/PQR on Time should be deleted in line with ISPE recommendation to defer. ISPE recommends that additional clarity would be beneficial for the requested		Please also see comments in Appendix 1

		data points to ensure consistency in interpretation across industry, such as: • Lots attempted • The number of lots attempted which are released for distribution or for the next stage of manufacturing the product. (Lines 549 and 550)		
	524 to 525	The sentence 'and that we understand is developed and maintained in the course of manufacturing drugs in compliance with current good manufacturing practice.' should be deleted.	Recommend deletion	Manufacturers may or may not be collecting similar metric data however currently it is unlikely that they will be collecting data to the FDA definition
	538	Delete ~~"The number of attempted lots pending disposition for more than 30 days. "~~	Recommend deletion	Lots that are not dispositioned in 30 days may not have open deviations or some other problem. They may be held for many other reasons that have nothing to do with product quality.
	540	Amend "….including stability testing."	To "…including stability testing **at labeled conditions and within expiry**."	OOSs at accelerated or stressed conditions or beyond expiry are not unexpected. Ideally, these studies are run until there is an OOS.
D. How to Report Quality Data to FDA	572 to 643 General Comments on section	ISPE recommends metrics data should be **submitted annually** to FDA without breakdown into quarters (line 578 and 579)		Please refer to answer to Question 2 in the FRN and Appendix 2
	585 to 586	'Any optional metrics would may be submitted using the same method described above.'	Delete 'may'?	Grammar/sense
	585 and 586	Reference to submission of Optional Metrics is recommended to be deleted		Please see discussion in Section 2 and Appendix 3
Alternative Approach for Comment ***Reducing the Reporting Burden***	600 to 606	ISPE recommends flexibility in the timing to report metrics data. This flexibility will be helpful to enable firms to align with internally established practices (e.g., APR schedule, Management Review) and consequently manage associated reporting burden		Such flexibility would reduce the burden

Based on Data Collection Timeframe				
	613	The phrase "…within the selected time frame." Requires definition		"selected time frame" is not defined. Allowing establishments to report according to the APR/PQR schedule is preferable. FDA would have to allow at least 25 months to allow for reporting cycles throughout the year. Reporting in quarterly segments will add significant additional burden and would only be useful on product with a significant number (e.g., 10 or more) of lots made per quarter.
Alternative Approach for Comment Including a Limited Text Field for Data Point/Metrics	619 to 643	ISPE recommends that a text field is included for the metric. This should be of sufficient size to allow firms to comment on both metric and data point, as appropriate. The size of the text box should be dictated from introduction of the program. It is strongly recommended that FDA take account of commentary when evaluating a firm's quality metric data.		Metric data are most valuable in the context of how the data are used and actions taken by firms. 100 words may not allow good explanatory commentary. As an example from one firm: "Generally each instance was described and this resulted in ~ 20 words per entry. Any reporting period would have multiple entries therefore in each period there were up to ~ 50 words per each entry" Extrapolating this (describe highlights within each quarter) to Reporting by quarters, would equate to minimum 50 words per quarterly data point resulting in a recommendation of up to 200 words for each annual data point.
Glossary	General			
	645ff	GLOSSARY doesn't contain "Quality Metrics".	ISPE recommends inclusion of "Quality Metrics" in GLOSSARY.	"Quality Metrics" should be defined clearly especially for the specific usage in this guidance.
	720			

Appendix A	General	An examples of an alternate template is given in Appendix 2		
	729 to 860			Completion of these data submission tables (presumably on line) is an example where a Pilot/start small would be extremely helpful. This was a key finding from ISPE Pilot Wave 1.
	852 to 860	'How is Product Specific Information worksheet linked to Mandatory Data worksheet?' requires explanation	How is Product Specific Information worksheet linked to Mandatory Data worksheet?	In the Guidance this is not clear. Recommend further explanation in the detailed submission Guidance

Section 4: ISPE Comments on FDA Federal Register Notice on Quality Metrics [Docket No. FDA-2014-D-2537]

Section	Page, Paragraph and Question	Comment	Recommendation and Rationale	Reference
	General	1. Supports FDA's effort to implement a Quality Metrics program 2. Supports the need for the program to start with a small, targeted approach 3. Recommends a phased introduction 4. Is supportive of starting with 3 of the proposed metrics 5. Recommends deferring as some metrics and data points 6. Considers the burden is underestimated 7. Requests greater transparency on manner in which data will be assessed, and outcome and conclusions determined	Please refer to Section 2	
Summary	p1, para 1	Explanation is required please of *'…how FDA intends to use quality metrics data to further develop the FDA's risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to*	Revise text and either remove reference to drug shortages or provide additional insight and clarity on the anticipated predictive nature of quality metric data as it relates to prediction of drug shortages **ISPE supports starting with reporting initially using**	Please refer to Appendix 4 for a discussion on ISPE's perspective on the **proposed** quality metrics data ability to assist predict potential drug shortages.

		improve the efficiency and effectiveness of establishment inspections, and to improve FDA's evaluation of drug manufacturing and control operations.' Explanation should be given in more detail.	**practices operated currently by most of industry**	
		ISPE supports strongly '*FDA expects that the initial use of the metrics will be to consider a decreased surveillance inspection frequency for certain establishments. For example, establishments that have highly controlled manufacturing processes have the potential to be inspected less often (as a lower priority for inspection) than similar establishments that demonstrate uncontrolled processes (as a higher priority for inspection). In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post approval manufacturing changes.*'		
I. Background	p4, para 3	ISPE considers that the following text refers to site-based issues. '…	ISPE supports starting with reporting initially using practices operated currently by most of industry, which	

		substandard manufacturing facilities or processes are discovered, or significant quality defects are identified in finished product, necessitating remediation efforts to fix the issue, which in turn, may interrupt production, and cause a shortage of drugs.'	focuses attention on site-based issues.	
II. Specific Request for Comments and Information	p7 (1) *Optional metrics related to quality culture and process capability/performance,*	ISPE recommends that FDA-proposed Optional Metrics are deferred and only considered when the program is established.	This is consistent with ISPE position that it: 1. Supports the need for the program to start with a small, targeted approach 2. Recommends a phased introduction 3. Is supportive of starting with 3 of the proposed metrics 4. Recommends deferring some metrics and data points 5. Considers the burden is underestimated More discussion relating to deference of Optional Metrics is given in Section 2.5 and Appendix 3	
	(2) *frequency of quality metrics data reporting,*	ISPE recommends metrics should be **submitted annually** to FDA	It should be recognized that any additional segmentation e.g., quarterly beyond annual will add to reporting burden for firms Reporting quarterly is likely to produce low values which will be difficult to interpret Affording flexibility in the timing to report metrics data will be helpful to enable firms to align with internally established practices (e.g., APR schedule, Management Review)	Please refer to estimates in Appendix 2. It is estimated that collecting data quarterly and submitting annually is 1.5 times more burden than collecting data annually (17.1 hours for one collection period compared with 25.1 hours for 4 periods)

	(3) *an alternative approach to reduce the reporting burden based on the data collection timeframe,*	ISPE recommends starting with reporting initially using practices operated currently by most of industry, which focuses attention on site-based issues. Reporting should be aligned with internally established practices (e.g., APR schedule, Management Review) to FDA	Consistent with the way industry mostly operates currently and hence minimizes the burden	
	(4) *an alternative approach that would allow inclusion of a limited text field for data points or metrics.*	ISPE recommends that a text field is included for the metric. This should be of sufficient size to allow firms to comment on both metric and data point, as appropriate. The size of the text box should be dictated from introduction of the program. It is strongly recommended that FDA take account of commentary when evaluating a firm's quality metric data.	Industry has found from many years of experience that interpretation of metric data requires commentary on individual metric data points and on trends. The commentary should be restricted to comments on or clarification of the data.	ISPE Pilot Wave 2 has as one of its objectives assessment of the value of trending and findings should become available in 2016
III. Comments	P7	None		
IV. Paperwork Reduction Act of 1995	p8, para 3 (1) *Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the*	ISPE considers that collection of quality metric data as proposed by ISPE will assist FDA with risk-based inspection scheduling. These data alongside other data and information available to FDA should help FDA to		

	information will have practical utility;	produce a risk-based inspection schedule. ISPE considers data submitted on a site basis as proposed by ISPE will also allow FDA to improve the efficiency and effectiveness of establishment inspections, and to improve FDA's evaluation of drug manufacturing and control operations. ISPE also considers that these quality metric data relevant to a site's performance alongside other information from the firm such as the quality of development information given in the application should support opportunities to develop more flexible regulatory approaches as discussed in Recommendation and Rationale section. ISPE is not aware of evidence that provision of quality metrics data for the 4 mandatory metrics proposed by FDA to be submitted on a product then site basis can assist with helping predict potential drug shortages. ISPE questions if the additional burden to report data on a product then site basis is justified.		ICH Q8 (R2) and ICH Q11 Please refer to Appendix 4

	(2) *the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used;*	ISPE considers that the FDA estimate of burden is low. ISPE's estimate based on preliminary data from Wave 2 is 2.4 times that of the FDA		Preliminary data from ISPE Pilot Program Wave 2 are given in Appendix 2
	(3) *ways to enhance the quality, utility, and clarity of the information to be collected;*	ISPE recommends that quality, utility and clarity will be achieved best if quality metric data for Lot Acceptance Rate and Invalidated OOS Rate are submitted initially on a site basis. The quality of the information depends on how clear the definitions for each of the metrics is for all involved parties. If definitions are clear to all then the quality and utility will be enhanced.	This approach is consistent with how many companies currently operate and implementation of ISPE recommendations will minimize burden and errors due to changes of reporting practices.	Appendix 2 Please refer to Section 2 and Appendix 1 for more discussion on the importance of clear definitions
	(4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.	ISPE has provided recommendations regarding how the burden can be minimized.	ISPE recommendations can be summarized as ISPE: 1. Supports the need for the program to start with a small, targeted approach 2. Recommends a phased introduction 3. Is supportive of starting with 3 of the proposed metrics 4. Recommends deferring some metrics and data points 5. Reporting annually and not quarterly	

		ISPE recommends that the Electronic Submissions Gateway (ESG) is thoroughly tested before it is exposed to the whole industry.	Could FDA provide the option of using CDER Direct to submit the quality metrics data? A company experience is: *"The FDA Quality Metrics draft guidance requests that all quality metrics data reports are to be submitted through the FDA Electronic Submission Gateway (ESG). FDA does not envisage that there will be any additional burden associated with using the ESG, because reporting establishments are already required to use the ESG for FDA establishment registration & drug listing. However, some companies do not have the resources and expertise to create the required Extensible Markup Language (XML) files in the Structured Product Labeling (SPL) format for submission directly through the ESG. Firms currently have to pay consultants to submit data on their behalf. Additional reporting of quality metrics through the ESG will therefore result in an extra financial burden.* *In September 2014, FDA launched a free, alternative on-line tool that allows pharmaceutical firms to create, review, save, and submit certain SPL files through the ESG without the need of the Web Trader account and digital certificates that are required for direct submissions through the ESG. This new system (CDER Direct) features a form-like data entry interface and provides tutorial slides, descriptive text, helpful links, and submission status. CDER*	

			Direct currently allows submission of establishment registration, drug listing, GDUFA self-identification, NDC/NHRIC Labeler code requests and Wholesale Drug Distributors & Third Part Logistics Facility Reports. The submission process of the quality metrics data would be enhanced if FDA could provide the option of using CDER Direct to submit the quality metrics data.	
	p9, para 1	Inspection frequency being linked to *'highly controlled manufacturing processes'* is not a good example. ISPE recommends that an example is created linked to quality metrics, the subject of this FRN.	Request clarification of the term *'highly controlled'* which is a new phrase and not defined. It is also not a quality metric proposed in the Draft Guidance. Hence how can it impact inspection frequency? Quality performance of a site is more than 'control' of processes Sites may have processes with a range of performance and have procedures and capability, which linked with 'good' quality metric data and other information may justify a reduced frequency of inspection.	
	p10, last line	Delete last bullet	ISPE recommends that APR/PQR on Time Rate is not included in the mandatory list of metrics for reasons given in ISPE's rationale to its Section 2 and Appendix 3	
	p11, first line	Delete first bullet	ISPE recommends that APR/PQR on Time Rate is not included in the mandatory list of metrics.	
	p11, second paragraph	ISPE recommends that FDA-proposed Optional Metrics are deferred and only considered when the program is established.	Please see rationale given in ISPE's rationale in Section 2 and Appendix 3	

V. Attendance and/or Participation at the Public Meeting B Questions to Stakeholders	P14 to 16 Q1 *Are there other objective metrics that FDA should request in advance of or in lieu of an inspection that FDA should collect to improve our understanding of products and establishments for purposes of more informed, risk-based inspection scheduling and identification of potential product shortages?*	Not at this time: • ISPE recommends starting small as proposed and expanding if needed as part of a phased introduction of quality metrics • FDA proposed metrics, with the exception of APR On Time, represent insightful metrics that can be most easily standardized across industry. ISPE recommends that at least 3 years data are collected and analyzed before changes to the initial program are considered.		(ISPE Pilot Project Wave 1 Report, June 2015) [3]
	Q2 *Are the definitions of the metrics and associated data requests selected adequate and clear?*	ISPE recommends that additional clarity is essential of definitions for the requested data to ensure consistency in interpretation across industry, such as: • Invalidated OOS Rate - nonstandard definition appearing to include a double normalization • "Specification-related rejects" – term "specification" can have very broad interpretation therefore		Further comments and questions relating to definitions are given in Appendix 1 of ISPE's response to the Draft Guidance

		request examples to ensure full understanding of intent • Finished Dosage Form • Lot – • Product Quality Complaints		
	Q3 *Are the metrics requested from each business segment/type clear and appropriate?*	Clarity is needed on definitions of business segments and/or other examples e.g., • FDF (Finished Dosage Form) • API (penultimate only, include Biological or biotech drug substance?). • Non-registered establishments • Atypical actives (some actives are excipients in other environments; e.g., calcium antacids)		
	Q4 *Should the Agency explore collecting metrics from high-risk excipient producers, and if so, which excipients should be considered high-risk and what metrics should apply?*	Not at this time: the proposed program is consistent with the objective of "start small, learn and evolve" The impact of critical excipients on product quality outcomes is best managed directly by manufacturers and can be detected through some of the proposed metrics such as Lot Acceptance Rate		
	Q5		ISPE does not have a view.	

	Should the Agency explore collecting metrics from the medical gas manufacturing industry?			
	Q6 *Should the Agency add the "Right First Time" metric (see section I.), and if so, should the definition be a rework/reprocessing rate or a measure of lots manufactured without processing deviations?*	Not at this time: the proposed program is consistent with the objective of "start small, learn and evolve"	Experience in the ISPE Wave 1 pilot indicated that it is a challenge to get to a standardized definition for this metric across industry. Additionally from an ISPE survey at a public meeting, only 65% of companies reported that they had a Right First Time metric. Consequently this metric was not included in ISPE Pilot Wave 1. Given FDA's continued interest in this metric, it was decided to include it in Wave 2 and findings should become available in 2016. ISPE considers that Right First Time is an appropriate metric for companies and sites to develop and use to drive their own continual improvement activities using their own definition appropriate to their own situation.	ISPE Pilot Project Wave 1 Report, June 2015 [3] and White Paper, December 2013 [5]
	Q7 *What data standards/mechanisms would be useful to aid reporting and how should the submissions be structured?*	ISPE recommends: Reporting data annually by **site** initially **for Lot Acceptance Rate and Invalidated OOS rate, and by product for Product Quality Complaint Rate.** **Providing data annually**	ISPE's rationale is given in Section 2.4 Minimizes burden	

		Allow for commentary **Providing transparency to analytics/algorithms /outcomes**	Industry experience is that metric data are not useful without an understanding of context **Trending of a site's performance** is more important than comparison of single values in isolation across sites and firms Trending manages the variability that could be introduced due to inconsistency in interpretation or reporting expectations 100 word limit for comments **may not provide sufficient context** for reported data – see earlier comments in response to questions in Section Allows industry to understand how their quality metric data are being interpreted/ resultant outcomes	
	Q8 *Are there reporting hurdles to collecting metrics by reporting establishment /product (segmented by site) versus by site (segmented by product), and how can they be overcome?*	Significant additional burden (3.3 times) for industry to report Lot Acceptance Rate and Invalidated OOS Rate data by product Evidence is required please to demonstrate how the proposed quality metric data at a product level, differentiated by site with annual reporting frequency enables prediction of drug shortages It will be important to show benefit from the reporting program and early benefits are most likely to be seen by		Please refer to Appendix 2

		focusing on the relationship between site data and risk-based inspection frequency Additionally as discussed in response to Question 2, definition of a product (finished dosage form) is a challenge, its definition being more important when it is the primary reporting data point.		Please see Appendix 1
	Q9 *FDA may consider whether to require the submission of quality metrics on a recurring basis. How frequently should metrics be reported and/or segmented within the reporting period (e.g., annually, semiannually, or quarterly)?*	Metrics are best **submitted annually** to FDA	Reporting to FDA metrics recommended by ISPE is optimally done annually. It should be recognized that any additional segmentation beyond annual will add to reporting burden (1.5 times) for firms Affording flexibility in the timing to report metrics data will be helpful to enable firms to align with internally established practices (e.g., APR schedule, Management Review) Low quarterly values for metrics data will be difficult to analyze and not justify the additional burden of collection and submission.	Please refer to Appendix 2

Appendix 1

Comments, Recommendations and Questions Relating to Definitions

Lot Acceptance Rate

- A lot is considered attempted when a lot number is issued for it. However, the lot numbers are more dependent on work flow/work order design rather than "release" considerations.
    - For example, many sites use lot numbers (or process order numbers) for tracking purposes for production steps that do not have a quality disposition at the end of the step. In these cases, a lot can be rejected for manufacturing deviations, but there is no release process. Should these lots be counted as "attempted" nevertheless?
    - Some companies are assigning lot numbers in smaller incremental manufacturing stages than others. For example, system-assigned tracking numbers may be assigned to a single batch as it moves through manufacturing stages. These tracking numbers may be serving as lot numbers. Further, sites with continuous processing may have one lot number assigned from end to end.
    - What is the definition of lot attempted for a packaged lot/packaging process?
- What does 'charged API' mean? Is it when the API that has been electronically set aside for the lot in the inventory system, API that has been weighed, or API that has been added to the batch? Recommendation is to consider API 'charged' once it has been added to the batch.
- Should lots rejected be counted for each period, regardless of whether they were attempted in another period, causing a mismatch, especially for products with high volume fluctuations and long processing times? Recommendation is to count lots rejected for the current reporting period, regardless of when they were attempted.
- What is meant by "specification-related" rejected lot? In some cases, there are quality-related rejections that are not directly related to drug product or drug substance specifications.
    - Should quality-related rejections for the following reasons apply?
        - Raw Material Specification
        - Product Specification
        - Component Defects
        - In Process Parameters
        - Operating Parameters
        - Environmental Monitoring Limits
        - Yield Limits
        - Storage Requirements
        - Lots Rejected due to Out of Trend Results
    - Additional examples of quality-related rejections are those that may result from spills, acts of nature, flow reversal in aseptic core, general upstream

GMP issues, and campaign batches that passed specification acceptance criteria but cannot be ruled out from an associated investigation
    - Does this include partial batch rejections? Recommendation is to include full batch rejections only.

- The Guidance is asking only for a subset of batch rejections (i.e., specification-related rejections), and so calling this metric "lot acceptance rate" is a misnomer as some rejections will go uncounted.
- There are a variety of practices on how rejections are categorized and reported at firms. It would be additional burden to segregate batches. On the other hand, there could be unintended consequences for companies being perceived as having high levels of rejection vs. making conservative quality decisions.
- Should rejections be counted based on the date of quality disposition or date of financial write off?
- The definition and use of pending disposition lots is not clear:
    - Should the 30 days be defined as calendar or working days?
    - Should the 30 days be counted after all manufacturing for the stage is completed and all testing results are available? Or should it be counted after end of manufacturing?
    - Should the count happen at the end of each reporting period (snapshot), or whenever a lot reaches 30 days within the reporting period (potentially more burden)?
    - Certain establishments e.g., CMOs require additional time for a full evaluation and client approval of any issues that may hold up disposition

Product Quality Complaints Rate

- Should released attempted lots serve as a normalizer for FDF complaints?
    - Number of complaints is related to the number of units the customer or consumer receives – which is sometimes packs, sometimes individual units
    - Alternatively, the finally released lots for shipment could be used – if we assume that their size is uniform and hence correlated to the final consumer units – it could serve to normalize complaints as well
    - However, released attempted lots as defined in the Guidance include those released after interim production stages, e.g., dispositioned lots after granulation or after blending. And since lots are frequently aggregated or split between stages, this number is not correlated with the finally dispositioned lots and even less with the customer end units.
    - For APIs, however, lot may be appropriate.

- What types of complaints are excluded, based on the definition “a complaint involving any possible, including actual, failure of a drug product to meet any of its specifications designed to ensure that any drug products conform to appropriate standards of identity, strength, quality and purity?”
    - Exclude Lack of Effect complaints? Other adverse events?
    - Exclude Customer Preference complaints? If yes, how are these defined?

- Exclude complaints later found to be on counterfeit product?
- Other?

- Many complaints are received without enough product information to associate with a single application number.
  - For example, complaints may be received that are associated with the brand name but not with a particular formulation. How should these be reported under individual applications? Report for each application where the complaint might be relevant or for just one, and if the latter, based on what criteria?
  - Could we manage this by reporting complaints at a product family level and not necessarily report each complaint at the US Product Application level?

- Total Complaint Rate is not meaningful if the goal is to correlate with quality system issues. It is challenging to determine 'real' from 'fraudulent' complaints, particularly for OTC products. Only a small percentage of complaints is confirmed as design or manufacturing issues - these are the best indicators for risk.

- FDA has not specifically defined "lots released."
  - Does "lots released" on Line 831 refer to the data point "the number of lots attempted which are released for distribution or for the next stage of manufacturing of the product" as stated on Lines 549-550?
  - Should lots released be counted for each period, regardless of when they were attempted in another period, causing a mismatch, especially for products with high volume fluctuations and long processing times? The definition should be clarified to say "in the current reporting period" rather than "in the same timeframe" (line 426) to avoid confusion.

Invalidated OOS Rate

- The normalization method outlined in the guidance involves double normalization against both total OOS and total tests. This means the metric will be a measure of laboratory error rates against volume, but will be skewed by the confirmed OOS, which is influenced by manufacturing excellence and product specifics. For example 2 labs with the exact same testing volume and the exact same number of lab errors may have different invalidated OOS rates if the tested products have different levels of quality OOS issues.

- Further clarity is needed on how to count in-process testing – if a test is repeated on intermediate and finished product, are both counted or just the latter?

- There are conflicting references to total tests performed: line 431/432 reads "…total number of tests performed *by the establishment…" vs.* line 542 which reads "…the number of lot release and stability tests conducted *for the product*…"

- Further clarity is needed on how to count 'tests'. For example:
  - Dissolution Stage 1: Six (6) results are compared individually against the specification but an average reported in CoA. Should we report 6 tests? Or should this be counted as 1 test?

- Content Uniformity Stage 1: Ten (10) results compared to specification acceptance criteria but average reported in CoA. Should we report 10 tests?

Recommendation: Report 1 test in both cases.

- Invalidated OOS Rate is not typically captured and consolidated at a product level, including in APRs. The value of these data at a product level is not clear. Reporting invalidated OOS Rate by product may require additional data gathering by sites and additional burden.
- When reporting data, the FDA requests "the number of OOS results for the product, including stability testing" (Line 540). Recommend modifying the request to state "the number of OOS results for the product, including stability testing *that supports marketed requirements*."

APR/PQR On Time Rate

- ISPE recommends removing this metric from the required metrics set. However, if FDA intends to move forward to require reporting, the term "annual due date" will need to be defined.
- ISPE recommends 30 days from the due date required by company procedure, rather than 30 days from the application approval anniversary date. CMOs will require additional time for a full evaluation and client approval of data.

Finished Dosage Form

- Is this one count or quantity of one formulation of a dosage form in a primary pack, all quantities in a one primary pack or a product family (e.g., multiple colors or flavors) in one or a range of primary packs? This point is not clear since one marketing application may contain all the above ranges in one application.
- One batch of bulk product could be packed into several primary packs and each primary pack could be labeled at different locations. Are data to be provided at bulk product, pack (NDC code) or labeler level? NDC level reporting or tracking would conceivably take the level of reporting to the stock keeping unit (SKU) level, which would be very time intensive. Conceivably metric data could be collected from all these levels e.g
  - Lot acceptance rate and Invalidated OOS at bulk product level,
  - Product complaint from pack (leaking bottle of liquid) – although torque of cap may not be in the (bulk) drug product specification, there will be limits applied to production and this probably fits within FDA definition
  - Product complaint from a label error. Again unlikely to be in a finished product specification in an application but nonetheless could produce a serious complaint and could fit with FDA definition. This complaint is at the labeled product level

Specification

- Throughout the guidance there is inaccurate use of the term 'specification'. 'Specification' is often applied to acceptance criteria for individual attributes rather

than '…a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described' as given in ICH Q6A and B (e.g., line 727). Where appropriate the term 'specification acceptance criteria' should be used.

Appendix 2

Burden

Burden estimates were based on preliminary submissions of Wave 2 Pilot data from 8 companies, and includes 40 product reports. The data was collected by product by site for the 3 mandatory FRN metrics. In addition to the small sample, in several areas the current estimate is likely to underestimate the effort due to:

- For the pilot most companies used products with small supply chains – over 60% of products are manufactured at a single site. That reduced their data collection effort per product and also the guidance and coordination effort compared to dealing with the full network
- The companies providing preliminary data are likely the ones whose systems make data collection easier
- Similar to Wave 1, a pilot context is not "official regulatory" submission and hence excludes senior management data review, verification & validation, legal reviews, and process to ensure reconciliation of all metrics back to data as reported to FDA

Based on that sample the effort for one product report will be on average 11.4 hours for pure data collection, plus 5.7 hours for overall guidance, coordination and review, hence 17.1 hours[1].

- For OTC products the average was 26.8 hours, for Rx/Gx products 12.9 hours
- The pure data collection effort was highest for products with complex supply chains and the guidance effort highest for companies outside of US and Europe

Extrapolating the data collection effort from annual data points to providing 4 data points per year (quarterly for annual reporting) was made using 3 assumptions:

- Assumption 1: for Lot Acceptance Rate splitting into quarters is considered very complicated due to mismatch between attempts and rejects counts (rejected lots can be for attempts made in earlier periods) – the effort was assumed to be 3 times the effort for single data collection[2]
- Assumption 2: for the other metrics the quarterly collection would add only approximately 20% effort over the annual one[2]
- Assumption 3: guidance time would not increase significantly, so it was assumed to stay the same

The annual effort based on these assumptions would be 19.5 hours average for pure data collection and 5.7 hours for guidance and coordination, to a total of 25.2 hours (17.4 for Rx/Gx, 43.5 for OTC)

[1] Including the collection of the data point "attempted lots pending disposition more than 30 days"
[2] Based on POBOS experience with repeat data collection at same site over years

Based on the FRN, there are expected to be 63000 product reports, which at 25.2 hours on average add up to 1.6 million hours. This is based on the collection of 8 data points, compared to FDA's full set of 15 from the FRN but the effort still exceeds the FDA estimate of 10.6 hours.

- "Pending Disposition" and "total OOS" data points represent 15% of the effort – removing or deferring their data collection will reduce the industry burden by approximately 230,500 hours, for a remaining total of 1.35 million hours

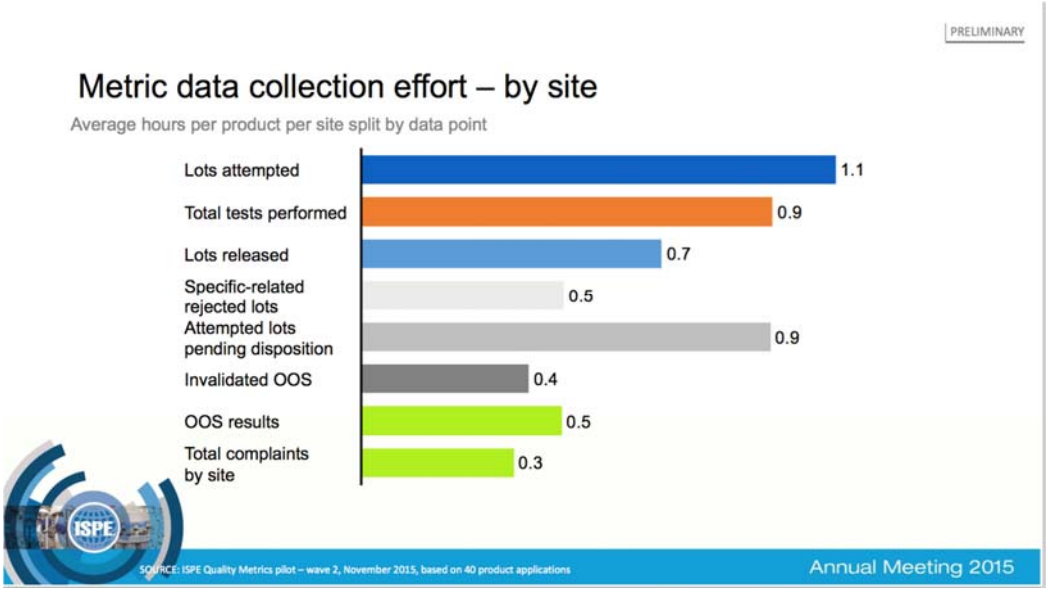
Wave 1 effort estimate for collecting lot acceptance rate, total complaints rate and invalidated OOS (with ISPE Wave 1 definitions) was 30.8 hours per site. For 12, 000[3] sites with FEI that translates to 370,000 hours annually

In summary:

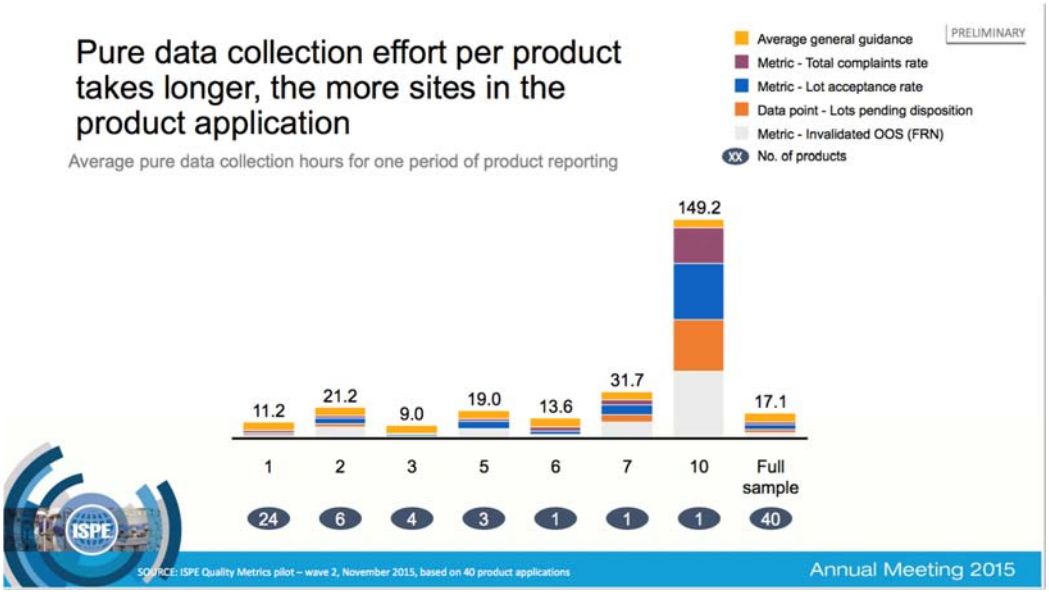
- ISPE is concerned that the FDA burden calculation estimate appears low. Wave 2 estimate of the burden to collect 8 data points (cf FDA 15 data points) is 25.2 hours on average compared with FDA's estimate of 10.6 hours "average burden per response" for 15 data points. ISPE's estimate is 2.4 times that of the FDA.
- Collecting data quarterly and submitting annually is about 1.5 times more burden than collecting data annually (17.1 hours for one collection period compared with 25.1 hours for 4 periods)
- Collecting data by product as in Wave 2 is estimated to add approximately 330% to the burden (3.3 times) compared to collecting by site (1.6 million by product compared with 0.37 million by site)
- Removing or deferring the data points of "lots pending disposition for over 30 days" and "total number of OOS test results" would reduce the total product burden by about 15%

[3] Based on Evaluate Ltd, as of Nov 6, 2015

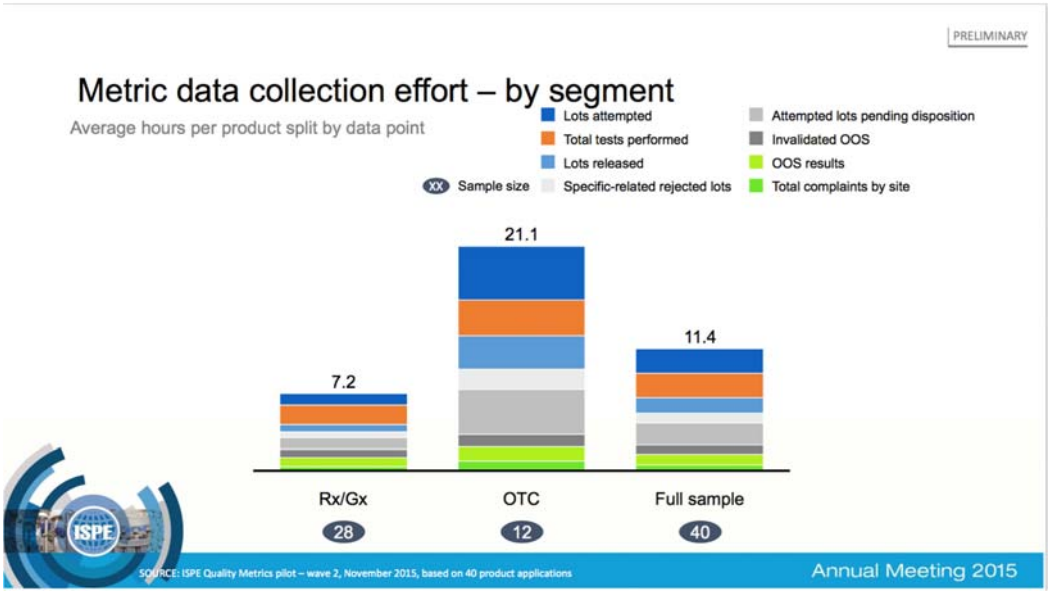
Data collection effort at site level of the individual data points are given in the following figure showing “lots pending disposition for over 30 days” data point is high (0.9 hours average per product)



Preliminary data from Wave 2 show increasing burden for one firm with a supply chain across 10 sites (149 hours per reporting period) compared with an average of 11 hours for products with only a single site



From the following figure, reporting of metric data for OTC products is nearly 3 times more resource on average than for Rx/Gx products



Appendix 3

Comments on APR/PQR on Time Rate and Proposed Optional Metrics

Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate

1. The APR/PQR metric as defined focuses on time and not quality and ISPE considers the metric would lead to unintended behavior.
2. Findings from ISPE Pilot Wave 1 indicate that APQR on time is not a highly differentiated metric with many sites reporting 100% achievement using the ISPE definition of Number of APQRs completed within the due date set by the company. Consequently it is considered provision of these data would not add value and not assist differentiating quality performance.
3. In ISPE Wave 1 there was not correlation with quality outcomes supporting the conclusion in point 2 above.
4. There are questions regarding definitions such as 'what is a drug product' for APR and what is the 'due date' for APR and PQR?
5. Why 'within 30 days of annual due date' rather than due date?

If APR/PQR on Time Rate is included in the initial metric set, please refer to questions and recommendations regarding the definition in Appendix 1.

The algorithm would be different for firms that do or do not provide Optional Metrics. Alternatively, only firms that supply optional metrics will be considered for reduced inspection schedule. If this is the case, FDA should be transparent and realistically Optional Metrics would then become mandatory for firms wishing to have the option of a reduced inspection schedule.

Consequently ISPE recommends this metric is not included in the final guidance.

Proposed Optional Metric 1:
Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither?

The question as proposed is likely to provide answers that are not related to a company's quality culture nor senior management engagement. It also has the potential to become a 'box ticking' exercise. For example:

- Signing of the APR(s) is not a true indicator of Senior Management Engagement and requesting this data point could have the unintended consequences.
- Senior management should ensure that the proper systems are in place to conduct appropriate annual product reviews, including appropriate review by subject matter experts. Additionally they have responsibility to ensure that proper resources are allocated to address CAPAs. Outcomes of APR's may be reviewed at Quality Council Meetings, Management Review meetings or other similar forum. Senior management

awareness and engagement of the follow up actions are more important than a signature on an APR.

ISPE questions what conclusions and next steps FDA will take from the range of answers that it receives.

Consequently ISPE recommends this optional metric is not included in the final guidance.

Proposed Optional Metric 2:
What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?

CAPA effectiveness should be evaluated by reoccurrence of similar deviation, complaint, OOS and other deficiencies.

Focusing on retraining as one outcome of a CAPA Effectiveness exercise is a very small element of quality culture and ISPE questions the value of this as an Optional Metric. The question as proposed is likely to provide answers that are not related to a company's quality culture

Even if other actions are taken, training is usually required making the proposed metric data difficult to interpret.

In ISPE Wave 1, the definition of CAPA Effectiveness was particularly difficult to achieve.

What is a good or bad number?

Consequently ISPE recommends this optional metric is not included in the final guidance.

Proposed Optional Metric 3:

- ***A "yes" or "no" value of whether the establishment's management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product's APR or PQR.***
- ***A "yes" or "no" value of whether the establishment's management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.***
- ***If "yes" to the above question – what is the process capability or performance index that triggers a CAPA? If "no" to the above question – please do not respond.***

Capability assessment should be part of a quality system element, and as such be part of a company's self-audit program. It can be used also to identify continual improvement opportunities and to support an improvement culture. Companies should be encouraged to use these tools in appropriate situations. They should not be reportable metrics for the following reasons:

- Choice of process capability tool depends on the situation, there is no one tool that can be applied to all situations

- There are not objective criteria agreed across the industry to judge an incapable process
- Not all CQAs have the same level of risk, nor are amenable to process capability calculations e.g., impurities near limit of detection (LOD)/limit of quantitation (LOQ), microbiological counts, test with multiple stages (dissolution)
- Cpk and Ppk typically cannot be used for all critical quality attributes
- Estimating process variability from a large number of lots gives different confidence intervals compared with a lower number. Many products are not manufactured sufficiently frequently to estimate true mean and standard deviation well.
- Cpk and Ppk values depend on quality attribute acceptance criteria in specifications and these acceptance criteria are established with reviewers based on judgments and limited number of batches. They are inconsistently established between attributes in same specification, between products in the same company and between companies. The concept of process capability as practiced in other industries is not consistent with the current control of variability in Pharmaceuticals.

Given this position 'yes' or 'no' answers to the questions provided by firms electing to submit are unlikely to provide meaningful information given the burden to report these data on a product-by-product basis and for each site.

There are also other valuable metrics to drive continual improvement in process robustness, for example the probability of OOS/percent defects.

Findings from the ISPE Pilot Wave 1 show:

- Process capability measurements are being adopted in the industry though there is no consistency yet in approach used**.**
- Usage: 95% of sites measure state of control during production process, most apply it to all products. Some exclude products based on risk approach to customer and importance for business.
- Metrics: Trending is most widely used – by 69% of sites. CpK, PpK and tolerance intervals less often – by 39% and 22% of sites respectively.
- Parameters measured: 91% of sites measure state of control through CQA, while only 56% on IPC and 61% on CPP.

Given that the sample demographic in the Pilot Wave 1 is skewed to companies with a good quality and compliance record, asking this question is unlikely to give higher values.

Further information on process capability will be available in 2016 from Wave 2 where these questions were asked.

Consequently, given that there is some burden to provide a response, ISPE recommends that process capability questions are not included in FDA quality metric requirements. It is perhaps more appropriate for "survey" type of questions to be asked at inspections if desired

ISPE would welcome explanation regarding what conclusions and next steps FDA will take from the range of answers it receives given that there are likely to be a large number of "no" replies based on experience from the ISPE Quality Metrics Pilot Program.

Consequently ISPE recommends this optional metric is not included in the final guidance.

Appendix 4

Rationale for Requesting More Explanation Regarding How Proposed Quality Metrics Data Can Assist Predicting Drug Shortages

ISPE does not have sufficient understanding of the manner in which the currently proposed metrics will assist with prediction of potential drug shortages.

ISPE suggests therefore that further exemplification of how FDA-selected metrics will assist with prediction of drug shortages. It is recommended that the Quality Metric Draft Guidance give examples or explanation (only statements given) of how FDA metrics selected are anticipated to aid in the prediction of drug shortages.

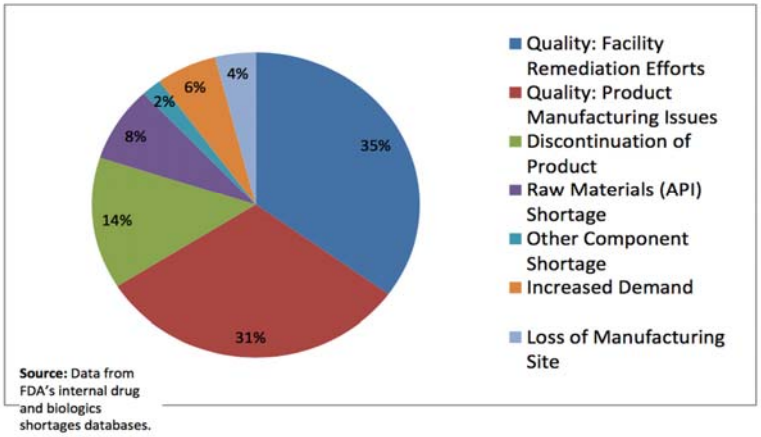
If not already completed, ISPE recommends that FDA assess the existing reported drug shortage data as source of information related to the anticipated predictive power of the proposed metrics. This evidence should be published.

Current available FDA documents are not clear on the manner in which the proposed quality metrics data can assist with prediction of drug shortages:

- Sections 704 to 706 of FDASIA do not make references to how use of data provided in advance of inspections can assist with prediction of drug shortages.
- The FDA Drug Shortages Strategic Plan [4] also does not exemplify or explain how the FDA quality metrics selected can help predict drug shortages.

The Draft Guidance (lines 150 to 151) and the FDA Plan in Figure 2 shows that 80% of shortages occur because of site-based issues.

Figure 2. Drug Shortages by Primary Reason for Disruption in Supply in 2012



All the examples of Root Causes of Drug Shortages in the FDA Plan are site-based.

FDA's Plan also recognizes that *'….shortages predominantly affect sterile injectable products….'*. Hence the rationale to extend the program to predict drug shortages to ALL products is not clear.

Quality metrics data proposed in the FRN and Draft Guidance will be quite lagging at point of receipt, analysis and action by FDA and more timely communication of potential drug shortage will have been provided by the FDA as required by current defined reporting requirements.

The metric that may be thought to have the potential to predict drug shortages, Lot Acceptance Rate, is lagging for detecting failure of specific lot or lots, which could then lead to drug shortages.

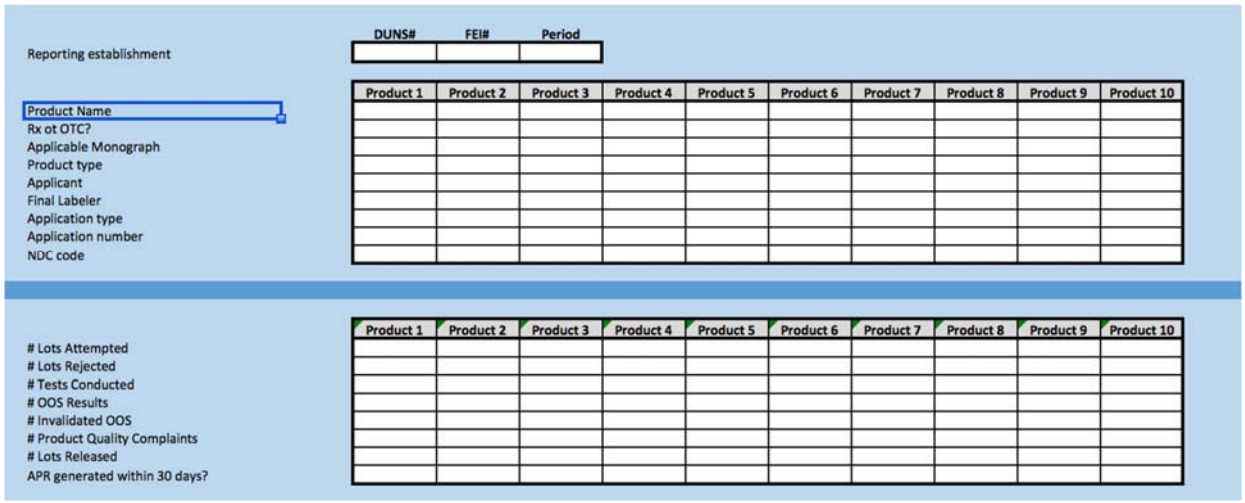
Firms which have relatively low values of Lot Acceptance Rate often take mitigating steps to minimize the risk of drug shortages such as:

- having higher stock levels
- monitor the supply chain more carefully.

ISPE's current perspective based on a review of the FDA drug shortages Strategic Plan [2] indicates that most drug shortages are due to site-based issues (page 11, para 3). For more detail, please refer to Appendix 4.

Appendix 5

An Example of a Revised Reporting Template - Site by Product



Reporting establishment	DUNS#	FEI#	Period

	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Product 8	Product 9	Product 10
Product Name										
Rx ot OTC?										
Applicable Monograph										
Product type										
Applicant										
Final Labeler										
Application type										
Application number										
NDC code										

	Product 1	Product 2	Product 3	Product 4	Product 5	Product 6	Product 7	Product 8	Product 9	Product 10
# Lots Attempted										
# Lots Rejected										
# Tests Conducted										
# OOS Results										
# Invalidated OOS										
# Product Quality Complaints										
# Lots Released										
APR generated within 30 days?										

References

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3. Report from ISPE Quality Metrics Pilot Project- Wave 1, June 2015, http://www.ispe.org/quality-metrics-initiative/pilot-program
4. Strategic Plan for Preventing and Mitigating Drug Shortages Food and Drug Administration October 2013, http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.
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