ISPE Comments – FDA Public Meeting August 24, 2015

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ISPE appreciates the opportunity to provide comments during the public meeting. Comments represent input from ISPE membership and are largely based on objective experience gained through Wave 1 of the ISPE Quality Metrics Pilot program.

Information is provided in the form of Key Messages (slides to be shared during the public meeting) and an Appendix containing answers to FDA questions. Additional comments and detail will be included in a submission to the docket.

Key Messages – Start small, learn and evolve

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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)
- Potential to provide early indicator of drug shortage (longer term)
- Risk-based principles for reduced post-approval manufacturing change reporting categories (longer term)

ISPE supports the need for the program to start with a **small, targeted approach**, to enable industry and FDA to learn and evolve the approach over time.

Recommend a **phased introduction**, for example:

- Start with higher risk facilities or products (eg medically necessary products with no alternatives)
- Start with FDF only, defer API reporting to later phase of program
- Start with voluntary reporting during initial learning period

Key Messages – Starting Metrics & Reporting Structure

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

- Lot Acceptance Rate (report by site, differentiated by product)
- Product Quality Complaints (report by product only)
- Invalidated OOS (report by site, differentiated by product)
- Additional clarity is needed on definitions (suggestions to be included in docket comments)

ISPE recommends to **defer as potential future metrics**

- APR on time
- Optional metrics related to Quality Culture and Process Capability/Performance

Start with **reporting by site, differentiated by product** (revise reporting templates)

- More representative of how industry currently gathering data
- May reduce burden for start up of program
- Acknowledge this may be more burdensome for contract manufacturers, contract laboratories

Key Messages – Reporting Burden & Transparency

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Burden appears significantly underestimated in FRN

- Reference to ISPE Pilot Wave 1 data
- Currently gathering additional case study examples in ISPE Pilot Wave 2
- Anticipated costs for firms to adjust internal IT systems and incorporate additional review and retention of data to support verification during inspection
- For many firms reporting by product, differentiated by site presents additional complexity and burden

Greater transparency required

- How data will be used (eg public disclosure, trending, comments for context, calculation of an aggregate “college board type” score for site or company comparisons)
- Link to algorithms for inspection scheduling and drug shortages
- Clarity on potential safe harbor period
- Communication to firms and understanding if their data has resulted in reduced inspection frequency (or reduced post-approval reporting)

Appendix

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Answers to FDA Questions

Comments on Proposed Metrics

Question 1

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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 :**
  - **Recommend starting small as proposed and expanding if needed as part of a phased introduction of quality metrics**
  - **Proposed metrics, with the exception of APR On Time, represent insightful metrics that can be most easily standardized across industry.**

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

(ISPE Pilot Project Wave 1 Report, June 2015)

Question 2

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Are the definitions of the metrics and associated data requests selected adequate and clear?

- **ISPE recommends that additional clarity would be beneficial 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 request examples to ensure full understanding of intent**
  - **Finished Dosage Form**
  - **Establishment**
  - **Lot**
  - **Product Quality Complaints**

Detailed comments will be provided in the submission to docket

Question 3

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Are the metrics requested from each business segment/type clear and appropriate?

- **Clarity is needed on definitions of business segments and/or examples to be included:**
  - **FDF (Finished Dosage Form)**
  - **API (penultimate only, include Biological Drug Substance?)**
  - **Non-registered establishments**
  - **Atypical actives (some actives are excipients in other environments; eg calcium antiacids)**

(ISPE Pilot Project Wave 1 Report, June 2015)

Question 4

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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**

Question 5

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Should the Agency explore collecting metrics from the medical gas manufacturing industry?

- **No – the proposed program is sufficiently extensive as a start. Program can be expanded later if needed.**
- **The impact of medical gas 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**

Question 6

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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. We believe it is an appropriate metric for companies and sites to develop and use to drive their own continual improvement activities.**

(ISPE Pilot Project Wave 1 Report, June 2015)

Question 7

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What data standards/mechanisms would be useful to aid reporting and how should the submissions be structured?

- Report data by **site, differentiated by product**
  - Collecting and analyzing metric data by site is current practice for industry
  - Site risk based inspection frequency planning is best accomplished by reporting data by site
- **Trending of a site's performance** is more important than comparison of single values in isolation across sites and companies and best manages the variability that could be introduced due to inconsistency in interpretation or reporting expectations
- **Transparency to analytics / algorithms** is requested
- 100 word limit for comments **may not provide sufficient context** for reported data

Question 8

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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 for industry to report data by product, differentiated by site – our estimate from Wave 1 data is indicative of same**
- **Evidence is required 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 focusing on the relationship between site data and risk-based inspection frequency**

Question 9

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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 should be **submitted annually** to FDA
- It should be recognized that any additional segmentation beyond annual will add to reporting burden for firms
- Affording flexibility in the timing to report metrics data will be helpful to enable firms to align with internally established practices (eg APR schedule, Management Review)

ISPE Comments on Optional Metrics

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ISPE does not recommend reporting on the optional metrics at the start of the program.

The proposed program excluding the optional metrics is consistent with the objective of "start small, learn and evolve" and can be expanded later if needed.

Detailed comments will be provided in the submission to docket